Innovatieve lokale drukmeting voor diagnostische
en therapeutische optimalisatie in verschillende orgaansystemen

Innovative Local Pressure Measurement Techniques
for Diagnostic and Therapeutic Optimisation in Organ Systems

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Proefschrift ingediend tot het behalen van de graad van
Doctor in de ingenieurswetenschappen: biomedische ingenieurstechnieken

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Preface

While working as an anesthesiologist in the past 14 years, I encountered multiple circumstances where the monitoring possibilities were significantly inadequate for optimally steering patient treatment and as every physician knows, we are virtually helpless without the technical devices and pharmaceuticals.

Out of these experiences, it became clear that there is a persisting need for more accurate and reliable monitoring devices in daily practice.

The purpose of the research is to develop practical technical solutions for diagnostic and therapeutic problems encountered in daily clinical work.

Thanks to my previous training in biomedical engineering, an inborn fancy for mathematics and informatics, and the unique opportunity for scientific collaboration with outstanding mentors, friends and research colleagues, I am grateful to have an opportunity to contribute to the advancement of medical equipment and treatment options.

With the here presented and ongoing research, I hope to offer innovative new solutions to ultimately improve future patient care.

Ghent, August 2016
Alain Kalmar

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Nederlandse Samenvatting

In de anesthesie en reanimatiegeneeskunde is een snelle en accurate diagnostiek van groot belang om de nodige interventies te kunnen verrichten. Dit is tijdens reanimatie een extra uitdaging omdat vaak moet worden gehandeld in ongeplande en onverwachte situaties, vaak in suboptimale omgeving, en onder sterke tijdsdruk. In deze omstandigheden is er pertinente nood aan verbeterde diagnostiek en bijhorende technieken om de interventies juist bij te sturen. Daarnaast moet ook de anesthesie de vernieuwingen in chirurgische technieken continu ondersteunen, en de nodige diagnostiek ontwikkelen om deze veilig te kunnen verrichten met vrijwaring van de fysiologische homeostase en het voorkomen van complicaties.

In vele klinische gevallen is het noodzakelijk om betrouwbare informatie te verkrijgen van fysiologische variabelen (zoals longen, hersenen of bloedbaan), liefst op een minimaal- of niet-invasieve wijze.

In het eerste deel van dit proefschrift wordt de techniek en het praktisch potentieel van nauwkeurige drukmetingen beschreven. Op basis van geavanceerde analyse van de dynamische drukmetingen kan waardevolle additionele informatie worden verkregen over het te behandelen orgaansysteem. De gebruikte hardware wordt beschreven, en de fysische en fysiologische principes die de basis vormen van de gebruikte analyses.

Het tweede deel van dit proefschrift beschrijft de medische problematiek van spoedintubatie in een reanimatiesetting, waarbij betrouwbare diagnostiek van de locatie van de beademingsbuis nog steeds een groot probleem is. In een maximaal gecontroleerde omgeving, zoals een operatiezaal, zijn de omstandigheden en technische hulpmiddelen beschikbaar om de een veilige werkwijze te garanderen. Bovendien zijn verschillende diagnostische hulpmiddelen binnen handbereik om foute intubatie snel te detecteren opdat snel bijkomende maatregelen kunnen worden genomen. In spoedomstandigheden buiten het ziekenhuis zijn de condities voor intubatie veel minder gunstig, en zijn de meeste technische hulpmiddelen niet beschikbaar. In dit hoofdstuk worden de belangrijkste problemen bij spoedintubatie besproken, en de belangrijkste beschikbare hulpmiddelen die hierbij worden gebruikt. Hierbij is bijzondere aandacht voor de beperkingen van deze hulpmiddelen voor gebruik buiten het ziekenhuis. Nieuwe hardware en analysesoftware wordt voorgesteld die aan de belangrijkste voorwaarden voor gebruik in deze setting poogt te voldoen.

Een ingediend octrooiaanvraag beschrijft de basisprincipes van een medisch hulpmiddel voor innovatieve drukmeting, en de software analyses voor een betrouwbare diagnostiek. Een eerste klinische studie bij patiënten onder narcose, beschrijft een validatie van de algoritmes voor automatische analyse van de locatie - in de luchtpijp of in de slokdarm - van de endotracheale tube. In deze studie werd de drukmeting verricht met katheters die in de endotracheale tube worden gelokaliseerd; de drukmetingen zijn uitgevoerd met conventionele medische druktransducers, gekoppeld aan een anesthesiemonitor; de drukgolven werden

continu geregistreerd op PC, en achteraf geanalyseerd met de automatische analysesoftware. De voordelen van het gebruik van drukmeting - in vergelijking met alternatieve technologieën - wordt toegelicht, en de onderliggende fysiologie waarop het algoritme is gebaseerd. De specifieke praktische voordelen van het algoritme worden besproken – in het bijzonder de snelheid van de diagnose, wat tijdens reanimatie van extra groot belang is – en het gebruik van elektronica die vlot kan worden ingebouwd in een draagbaar toestel. Deze studie toont de hoge betrouwbaarheid aan van het algoritme om bij mensen met gezonde longen de locatie van de endotracheale tube te identificeren.

In de vervolgstudie wordt een ontwikkeld draagbaar toestel geëvalueerd bij patiënten met longziekten op intensieve zorgen. In het apparaat is het algoritme verder geoptimaliseerd voor volautomatische analyse met directe melding van de diagnose. Deze studie bevestigt enerzijds de accuraatheid in patiënten met longpathologie, en toont anderzijds de mogelijkheid van een volledig "stand-alone device" om op basis van de voorgestelde techniek een nagenoeg ogenblikkelijke diagnose te leveren met minimale nood voor interventie van de gebruiker.

Naast het vrijwaren van een vrije luchtweg, is een tweede belangrijke doelstelling binnen de urgentiegeneeskunde het optimaliseren van cardiorespiratoire reanimatie (CPR). De principes hiervan worden toegelicht in het volgende hoofdstuk, met nadruk op het belang van de intrathoracale drukveranderingen, en het potentieel van de correcte meting hiervan om verdere optimalisatie van CPR mogelijk te maken. De technologie hiertoe staat beschreven in een tweede octrooiaanvraag. In een klinische observationele studie bij patiënten tijdens reanimatie wordt de techniek gebruikt om hartmassage te kwantificeren aan de hand van de intrathoracale drukmetingen.

Het derde deel van dit proefschrift beschrijft de problematiek van drukverhogingen in de hersenen tijdens neuro-endoscopie, en de noodzaak voor correcte meting hiervan. Een eerste artikel toont het gebruik van transcraniële Doppler voor het inschatten van de hersendoorbloeding tijdens neuro-endoscopie, en de beperkingen van de conventionele manier van drukmonitoring bij deze procedures. Dit illustreert de nood voor een betere diagnostiek om op een veilige manier conventionele neuro-endoscopische procedures te verrichten. Bovendien is er een specifieke vraag van de neurochirurgen om de kunnen spoelen met hogere druk, om hierbij meer complexe chirurgische procedures op minimaal-invasieve wijze te kunnen uitvoeren. De intra-operatieve drukmetingen die nu gebruikt worden tijdens endoscopische neurochirurgie tonen afwisselende periodes waarbij uiterst hoge intracraniële druk voorkomt. Hoewel het mogelijk is de druk te meten met de beschikbare hulpmiddelen, geeft deze conventionele methode vaak slechts heel onnauwkeurige metingen, wat een vertraagde diagnose oplevert bij gevaarlijk hoge intracraniële druk. De ontwikkeling en evaluatie van een nieuwe methode voor dergelijke drukmetingen die bruikbaar is in de klinische praktijk wordt getoond. Dit opent de mogelijkheid om meer geavanceerde neuro-endoscopische procedures met hogere spoeldruk te kunnen verrichten onder veilige controle van de intracraniële druk. Een derde octrooi toont het ontwerp van de gebruikte nieuwe techniek. Op basis van deze principes en chirurgische omstandigheden, tonen we een experimenteel model waarin de klinische neuro-endoscopische procedures kunnen worden

gesimuleerd met potentieel gewenste spoelsnelheden. Dit laat toe de nodige metingen te doen om het nieuwe device te evalueren. In een in-vitro studie wordt deze techniek uiteindelijk vergeleken met de conventionele methode van drukmeting.

Een vierde deel behandelt het gebruik van dezelfde basisprincipes, in combinatie met nieuw ontworpen connectiesystemen om tot een prototype te komen van een nieuw medisch hulpmiddel voor adaptieve centraal-veneuze drukmonitoring en -medicatie toediening. De huidige techniek voor centraal-veneuze toegang wordt beschreven, met haar beperkingen, gevolgd door een vierde octrooi waar een nieuwe technologie wordt voorgesteld die aan een aantal nadelen van de conventionele methodes tegemoet komt.

Vervolgens worden de principes toegelicht waarop de werking van het kathetersysteem is gebaseerd, en de productiemethode die gebruikt is voor de ontwikkeling van de prototypes in de eerste experimentele setups. De fysische eigenschappen die nodig zijn om te voldoen aan de klinische vereisten – in het bijzonder stroomweerstand en de vlotte plaatsing – worden besproken, en de vraagstukken die hierbij moeten worden opgelost om aan deze voorwaarden te voldoen. De materiaalkeuze en computer-geassisteerde ontwerptechnieken worden toegelicht, alsook aspecten van biocompatibiliteit waaraan moet worden voldaan om aan de technische vereisten te voldoen.

In-vitro en in-vivo tests beschrijven de eigenschappen van de nieuwe methode in het licht van de belangrijkste klinische vereisten. Vervolgens wordt een uitgewerkt prototype voorgesteld voor klinisch gebruik.

In het laatste hoofdstuk worden een aantal uitdagingen beschreven die nog moeten worden aangepakt om de hier beschreven prototypes tot een praktisch bruikbaar hulpmiddel uit te werken.

Summary in English

In anesthesia and resuscitation, a fast and accurate diagnosis is of critical importance to initiate the necessary therapy. During resuscitation, there is the additional challenge of mostly unplanned and unexpected conditions, often in a suboptimal environment and under strong time pressure. In these circumstances, there is a pertinent need for improved diagnostics to optimise the interventions. In addition, the innovations in surgical techniques, must be supported by refinements of the anesthesia, in order to accommodate these developments, safeguard the physiological homeostasis, and prevent complications.

In many cases it is necessary to obtain reliable measurements of physiological variables (such as lungs, brains or bloodstream), preferably in a minimal- or non-invasive manner. The first part of this thesis describes the technology and the clinical potential of more accurate pressure measurements. Based on advanced analysis of the dynamic pressure measurements, valuable additional information can be obtained about the organ system to be treated. The used hardware is described, and the physical and physiological principles that form the basis of the used analytics.

The second section of this thesis describes the difficulties encountered during emergency intubation where reliable diagnosis of the location of the breathing tube is still a significant problem. In controlled environments like the operating theatre, conditions and technologies are optimised for maximal safety. In addition, many diagnostic tools are available for fast recognition of the need for additional intervention. Most of these conditions are absent in emergency situations, as the medical devices used in hospitals are largely unfit for use in these out-of-hospital conditions. The particular challenges for safe endotracheal intubation, and the main available devices to assist in intubation and diagnosis are discussed and the limitations of these devices are shortly explained, with an emphasis on the pre-hospital conditions. New hardware and diagnostic software is proposed that aims to satisfy the most important requirements for use in this setting.

A filed patent describes the basic principles of a medical device for innovative pressure measurement, and the analysis software for reliable diagnostics. A first clinical trial in patients under anesthesia describes a validation of the algorithms for automatic analysis of the location - in the trachea or the oesophagus – of the endotracheal tube. In this study, the pressure measurement was carried out with catheters that are located in the endotracheal tube; the pressure measurements were performed with conventional medical pressure transducers, coupled with an anesthesia monitor; the pressure waves were continuously recorded on a PC and analysed afterwards with the automatic software. The benefits of the use of pressure measurements - in contrast with alternative technologies - are explained, and the underlying physiology on which the algorithm is based. The particular advantages of the algorithm are discussed, such as the speed of diagnosis - which is highly critical during resuscitation - and the reliance on potentially portable electronics. This study demonstrates the high reliability of

the algorithm in order to identify the location of the endotracheal tube in people with healthy lungs.

In the subsequent study, a portable device was developed and evaluated in patients with lung diseases in intensive care. In this device, the algorithm is optimized for automated analysis with immediate reporting of the diagnosis. This study firstly confirms the accuracy in patients with lung pathology, and secondly shows the possibility of a fully automatic "stand-alone device" to provide a basically instantaneous diagnosis requiring minimal operator intervention utilising the proposed technique.

In addition to securing the free airway, a second important objective in emergency medicine is to optimize cardiorespiratory resuscitation (CPR). The principles of which are explained in the next chapter, with emphasis on the importance of the intrathoracic pressure changes, and the potential of its correct measurement to further optimize CPR. Next, a second patent is described, demonstrating a technology to do this. Finally, in a clinical observational study in patients during the resuscitation, this technique is used to quantify chest compressions by making use of the intra- thoracic pressure measurements .

The third section of this thesis describes the problem of pressure increase in the brain during neuro-endoscopy, and the need for its accurate measurement. The first article shows the use of transcranial Doppler for the assessment of cerebral blood flow during neuro-endoscopy, and demonstrates the limitations of the conventional way of monitoring the intracranial pressure during these procedures. This illustrates the need for better diagnostics to safely perform the conventional neuro-endoscopic procedures, and certainly to allow more advanced use of high-pressure rinsing - which is desired by some neurosurgeons to permit more demanding surgical manipulations. The conventional intra-operative pressure measurements used during endoscopic neurosurgery demonstrate intermittent episodes with very high intracranial pressure. While feasible to perform with available devices, the conventional method provides very inaccurate measurements, with often delayed diagnosis of dangerous pressure levels. Because accurate pressure measurements are a prerequisite for advanced surgical techniques, a new device was developed and tested in order to obtain such measurements in a practical manner in clinical practice. A third patent shows the design of an alternative technique in order to perform those more accurate measurements. Based on the proposed principles and surgical challenges, an experimental setup was built to simulate the clinical neuro-endoscopic procedure with relevant rinsing flow rates, that allows the necessary measurements to evaluate the new device. An in-vitro study is described where the new technique is compared with the conventional method.

A fourth section discusses the use of the same basic principles, combined with redesigned connection systems to produce a prototype of a new medical device for adaptive central-venous pressure monitoring and medication administration. The current technique for central-venous access is described, with its limitations, followed by a fourth patent where a new technology is proposed which meets a number of disadvantages of the conventional methods.

Subsequently, the principles on which the device is based are explained, and the production methods used to develop early prototypes of the first experimental setups. The physical properties that are required to address the clinical needs – most importantly flow resistance and ease of insertion – are discussed, and the challenges that must be met to comply with these constrains. Material choice and computer-assisted design techniques are explained, together with biocompatibility concerns that limit choices to realise the technical objectives. In-vitro and in-vivo tests describe the properties of the new method in relation to the main clinical requirements. Finally, a developed prototype is suggested for clinical use.

The final chapter describes a number of challenges that need to be addressed to transfer the described prototypes into a clinical usable medical device.

I

Introduction

1

I1 Pressure measurements in medicine

In anesthesia and intensive care medicine, medical management often relies on pressure measurements. Most known is the blood pressure measurement, wherein the pressure in the arterial system is measured. Throughout medical history, a gradually growing understanding showed that a more detailed assessment of the blood pressure can provide more clinically useful information.

A more accurate measurement includes two aspects: on the one hand a higher accuracy and higher reliability of the absolute value of the measurement is important in order to optimize the management. On the other hand, in addition to the single pressure value, a continuous measurement at a high sample rate permits to extract additional valuable information from the blood pressure signal.

A illustrative historical example of this is the blood pressure measurement: After the first quantitative description of the blood pressure by Stephen Hales (18th century), and the development of the more convenient mercury manometer by Poiseuille (19th century), the first clinically useful non-invasive cuff -manometer was developed by Scipione Riva-Rocci in 1896. This device could however only display the systolic blood pressure, and therefore gave one number as a blood pressure value. A first refinement has been realized by Nikolai Korotkoff, which enabled to also determine the diastolic blood pressure. This is today the most used way to quantify blood pressure. As such, while blood pressure measurement per se was known for more than a century, it became only clinically useful after improvements in (non)-invasiveness and accuracy.

The development of a number of technologies that permit measurement of a continuous blood pressure signal in a minimally-invasive way makes it not only possible to obtain a much more accurate measurement of the diastolic and systolic blood pressure, but also enables analysis of

the pressure waveform. Computerized analysis of this signal permits to derive more advanced hemodynamic information, allowing significantly improved goal-directed therapy.

Similarly, In the applications discussed in this thesis we attempted to obtain improved diagnostics by making use of new possibilities in signal analysis, materials science, and physiological insights.

In the first application, a continuous pressure measurement in the endotracheal tube is used by an algorithm to provide a fully automatic diagnosis of the location of the tube. This diagnosis is based on accurate continuous pressure measurement and an automatic algorithm, which utilizes the physiological differences in compliance between the lungs and the stomach for a fast and accurate diagnosis. In addition, the same hardware also permits to extract other diagnostic information from the pressure signals for the optimization of the CPR by making use of dedicated algorithms. Ventilation rate, compression frequency and thoracic pump efficacy are some of the demonstrated applications.

In a second application in neuro-endoscopy, an accurate measurement of the intracranial pressure is essential to permit timely intervention when dangerous intracranial hypertension occurs, in order to prevent cerebral damage or bleeding in the eyes. The conventional techniques of intracranial pressure measurement are invasive or inaccurate. The new proposed method reports a very accurate pressure measurement in a non-invasive manner. Moreover, its a high sampling rate in addition to an accurate absolute measurement value also permits advanced waveform analysis to extract additional information on the intracranial hemodynamic conditions.

A third application relates to central venous pressure measurement, which is routinely used to guide the fluid management and pharmacologic therapy. A new device is described to switch the central venous catheter in a simple and non-invasive manner from a single-lumen to a multi-lumen system, or vice versa. This permits an accurate central venous pressure measurement while simultaneously medication is administered on other lumens. This alternative to the conventional procedure of replacing central venous catheters reduces the risk of several possible complications, simplifies the procedure, and as such permits to quickly adapt the number of lumens to the clinical need.

2

I2 Pressure measurement to guide therapy

In many medical domains, and particularly in the field of anaesthesia and emergency medicine, real-time diagnosis is essential to permit immediate therapeutic intervention. The primary aim of a medical intervention can be defined as restoring or preserving the homeostasis of the body. As such, fast quantification of critical physiological values is essential to permit a targeted intervention. Such interventions in these domains are often aimed at preserving mass transport within the body: blood through organs, or air to the lungs. These mass flows are driven by pressure gradients between two locations. While it is only one of the determinants of the true physiologic condition, the ease of measurement made pressure values historically the most used unit to assess the physiological conditions of the hemodynamic system and many organ systems.

> *"It is a source of regret that the measurement of flow is so much more difficult than the measurement of pressure. This has led to an undue interest in the blood pressure manometer. Most organs, however, require flow rather than pressure."*
>
> ***Jarisch A. Kreisslauffragen. Dtsch Med Wachenschr 1928;54:1213.***

Advanced computation of pressure waveforms can provide additional information on the physiological status of a particular organ systems: This consists of waveform analysis of pressure changes over time (dP/dt), and pressure differences between two locations (ΔP).

Conventional pressure measurements in vivo are used to assess the arterial and venous blood pressure, intracranial pressure, pulmonary pressure, intra-abdominal pressure or rarely at other locations using a rigid pressure tubing connected to a pressure transducer.

In this doctoral thesis, advanced in vivo pressure measurement techniques, and the necessary hardware and software were developed to improve the diagnostic value for therapeutic intervention in different organ systems.

In this introduction, three parts are considered:

1. The physiological principles applied in the developed concepts.
2. The instruments and technology used for the development of the devices.
3. The clinical applications for the new devices.

3

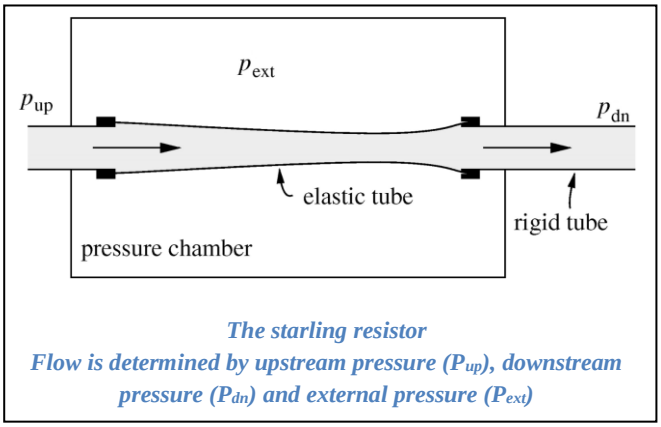
I3 Physiological principles

I3.1 Compliance and elastance

When in a closed volume - such as the lungs - the pressure is increased (ΔP), the degree to which the organ distends (ΔV) is the compliance $C = \frac{\Delta V}{\Delta P}$. The compliance of the organ at any given time during the change in volume is defined as the dynamic compliance $C_{dyn} = \frac{dV}{dP}$. Elastance is the reciprocal of compliance, hence the change in pressure for a given change in volume. Measurement of the dynamic compliance of either lungs, central venous system, cerebrospinal fluid or arterial vessels can yield critical diagnostic information.

I3.2 The starling resistor

The driving force of blood/air flow is the difference between upstream and downstream pressure of the system. In a rigid tube, the flow will therefore be determined by the pressure difference between inflow and outflow. In a tube with a collapsible wall however - such as (venous) blood vessels or bronchioli - an external pressure around the collapsible part may become predominant if the pressure in the vessel drops below a threshold value. In many medical conditions (e.g. obstructive pulmonary diseases), or during resuscitation (coronary perfusion) and surgery (neuro-



The starling resistor
Flow is determined by upstream pressure (P_{up}), downstream pressure (P_{dn}) and external pressure (P_{ext})

endoscopy, laparoscopy), this can become a major determining factor of organ perfusion/air flow.

The perfusion pressure is the pressure driving blood through the vascular bed, and therefore the difference between inflow (arterial) and outflow (venous) pressures. When, however, an organ (such as the brain) is contained within a rigid enclosure (the scull), an increase in extravascular pressure (the intracranial pressure) will immediately result in a force compressing the vascular system. As long as the intravascular pressure is higher than the extravascular pressure, the perfusion pressure remains $\Delta P = P_a - P_v$. Conversely, once the intracranial pressure becomes higher than the venous pressure, the veins collapse and act as a Starling resistor: $\Delta P = P_a - P_{ic}$. Equivalent effects occur during laparoscopy, intracranial neuro-endoscopy, and cardiac/pulmonary perfusion during CPR. Therefore, a third local pressure measurement - in addition to arterial and venous pressure - is necessary to determine the driving pressure of blood flow.

$$\Delta P = P_a - P_v$$

or

$$\Delta P = P_a - P_{ic}$$

Perfusion pressure

I3.3 From pressure to flow

Poiseuille's law describes that a steady laminar flow of an incompressible fluid through a pipe of constant circular cross-section that is substantially longer than its diameter induces a pressure difference over a length L, which is directly proportional to the flow Q. Therefore, a measured pressure difference over the length of a tube gives an estimation of the flow through the tube. In the proposed research, this principle is used for estimating the flow of air through a ventilation tube.

$$\Delta P = \mathrm{R} \times \mathrm{Q} = \frac{8\mu \mathrm{L}}{\pi r^4} \times \mathrm{Q}$$

Hagen-Poiseuille equation

or $$Q = \frac{\Delta P \pi r^4}{8\mu \mathrm{L}}$$

The equation indicates that the radius (to the forth power) is one of the principal determinants of blood flow and even small changes in lumen diameter will have significant effects. It is by this mechanism that vascular resistance can change rapidly to alter regional and global blood flow[1]. Still, for a given degree of vascular resistance, the flow is directly proportional to the pressure difference. This principle is valid for the vascular resistance as well as the resistance of an organ.

I3.4 From pressure to compliance

$$C = \frac{\Delta V}{\Delta P}$$

Compliance

During ventilation of the lungs, or during endoscopic flushing of the cerebral ventricles, air/fluid flows through a tube into the organ. The compliance of a hollow organ is not a constant value, but is dependent on the volume that it already contains. Typically, the more an organ is stretched, the less additional volume it will accept for a further increase in pressure. Therefore, assessment of the compliance gives an estimate of the physiological properties and condition of the organ.

1. Based on two pressure readings over a distance inside the tube (ΔP), the flow Q is estimated using Poiseuille's law.
   This calculated flow Q can also be written as: $Q = \frac{dV}{dt}$
2. The pressure change over time at the distal end of the tube (= inside the organ of interest) is measured:
   $\delta P = \frac{dP}{dt}$
3. The flow through the tube, divided by the pressure change in the organ equals the compliance. This is obtained as:
   $\frac{Q}{\delta P} = \frac{\frac{dV}{dt}}{\frac{dP}{dt}} = \frac{dV}{dP} = Compliance$

I3.5 From pressure to Volume

During surgery or other medical events, significant changes in blood volume may occur - either directly due to blood loss, or indirectly due to extravasation of intravascular water to the interstitium, or other losses. It is imperative to keep the blood volume available for the heart within physiological boundaries in order to preserve homeostasis. Direct measurement of the total available blood volume however is very difficult in clinical context, but (dynamic changes in) arterial and/or venous pressure measurement give an acceptable estimate of the fluid status of the patient. Reliable assessment of variations in central-venous blood pressure measurements are consequently often used to guide fluid therapy.

4

I4 Equipment and methods

The new devices developed permit improved diagnostic and therapeutic appliances based on advanced pressure measurements. The hardware to achieve the goal of reliable assessment of the desired physiological information in a clinical setting needs to comply with several preconditions such as accuracy, high sampling frequency, medical safety, easy implementation and high reliability in clinically demanding circumstances, disposable and preferably be cost efficient. Common electronic pressure transducers, and associated pressure tubings can comply with these preconditions, if a fitting architecture is combined with a suitable mathematical approach of the physiological casus.

I4.1 Pressure transducers

A semiconductor pressure transducer is an electronic component that generates an electric signal as a function of a mechanical pressure imposed on the component. Several technologies exist to build pressure transducers, depending on the desired specifications.

Fig 1: Universal disposable medical pressure transducer. The fluid connectors (at the left) are connected to an invasive catheter, which conducts the pressure to the pressure transducer (black square). This electronic component receives a DC excitation voltage of 5V on two wires. On the two other wires, voltage is measured by the monitor, with a sensitivity of 5 µV/V/mmHg. (e.g. a blood pressure of 130 mmHg and an excitation voltage of 5V delivers a voltage of 3,25 mV)

The semiconductor pressure transducers used are economical, small, consume very little power – allowing for battery-powered hand-held devices, and permit reliable sapling rates up to at least 250Hz.

Architecture of the used pressure sensors

Depending on the reference pressure used to quantify the measured pressure, several types of pressure sensors exist. ❶ The absolute pressure sensor measures the pressure relative to the perfect vacuum. Negative absolute pressure is therefore non-existent. ❷ The differential pressure sensor measures the pressure difference between two locations. ❸ The gauge pressure sensor, which is a differential pressure sensor in which one side is open to the ambient atmosphere. This type is universally used in medical applications, and also in this research. With gauge pressure sensors, negative pressures often occur, for instance during inspiration, where a negative gauge pressure in the thorax drives the atmospheric air into the lungs.

Different pressure-sensing technologies are used to convert a mechanical pressure to an electronic signal. In medical applications, the force collector type is predominantly used. These sensors use a force collector (such as a diaphragm) to measure strain or deflection due to the applied pressure over an area. The displacement of the force collector can be translated to an electronic signal trough different physical principles such as capacitive properties (changes in capacitance when pressure deforms the diaphragm), or electromagnetic, piezoelectric, or optical properties. In medicine, the most commonly employed force collector sensor is the piezoelectric strain gauge, which uses the piezoresistive effect: the resistance of the element changes as pressure deforms the material.

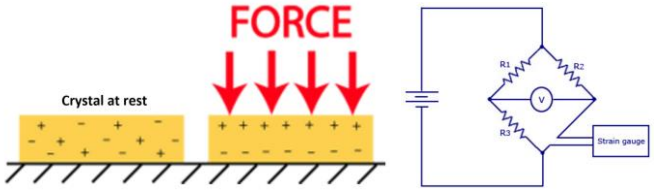


Fig 2: The Piezoelectric strain gauge.
An Applied force induces stress in the crystal, driving negative and positive ions onto opposed surfaces. The amount of accumulated charge is directly proportional to the applied force, and changes the electrical resistance of the sensor. This can be measured very precisely when configured into a Wheatstone bridge circuit.

Ultimately, the pressure transducer generates an electronic signal as a function of the exerted pressure. This signal must be further processed to yield diagnostic value.

Clinical embodiment of the used pressure sensors

Measuring the pressure inside a specific organ/body can be approached by two methods:

1. An electronic sensor directly placed inside the body.
   The pressure is locally converted into an electric signal. The main restriction of this approach is the location of the electronic device inside the body. This raises many biocompatibility issues, and often needs expensive devices.

2. A pressure tubing (catheter) is inserted in the body, through which the pressure is guided via a fluid or gas medium to an external pressure transducer.

This is often more practical, less invasive, and allows for cheap disposable pressure tubings to be connected to reusable/disposable electronic devices. The principal disadvantage of this approach is the added sources of artefacts. The impedance of the tubing system can modify the signal of dynamically changing pressure values:

❶ While an ideal pressure sensor has no internal compliance (= no internal volume shifts due to pressure changes), in practice a small volume shift in the pressure sensor embodiment itself does occur. This restricts the minimal internal diameter of the pressure tubings.

❷ The pressure tubings are rigid, but still have a certain compliance. When a compressible medium (such as air) is used in the pressure tubings, an additional increase in compliance follows.

❸ An additional risk of clogging of the tubings further restraints the dimensions of the pressure tubings within certain values, particularly when fast pressure changes, or high frequency oscillations need to be monitored.

I4.2 Pressure tubings

The pressure must be conducted from the location of interest (in the body) to the external semiconductor sensor using pressure tubings. Depending on the mechanical properties of the conduction medium (water, air, …), the clogging risk, and the dynamic pressure changes to be monitored, the internal diameter of the tubings and the rigidity of the material must be within certain boundaries. Because none of the applications proposed in this thesis is currently commercially available, material choice and dimensions of the tubings still had to be determined.

❶ In the device developed for monitoring intrathoracic pulmonary pressure (chapter II), the conducting medium is air. Because of the compressible nature of air and a significant internal volume of the pressure transducer, a certain volume of air must flow through the tube to permit proper pressure transduction. Since accurate pressure waveform assessment with a sampling rate of at least 50Hz is required, and because there is a high clogging risk (with saliva/mucus), tubings with relatively high internal diameter are required. This type of pressure measurement through the endotracheal tube was never reported before. Therefore a suitable dimension had to be determined, allowing accurate pressure readings through the catheter, while minimally obstructing the airflow through the endotracheal tube. We made use of polyethylene disposable catheters with an internal diameter of 1mm.

❷ In the intracranial pressure monitoring system (chapter III), only slow-changing pressures over several seconds must be monitored. In addition, a very small outer diameter catheter is desired, since it must be advanced through a neuro-endoscope with minimal obstruction of the rinsing channel. For the in-vitro flow study, an electronic tip-sensor was used to ascertain an accurate measurement. In addition, a very small, fluid filled polyimide catheter was selected as an economic alternative. This rigid polymer permits very thin-walled catheters, resulting in a minimal outer diameter for a given inner diameter while preserving the desired mechanical properties. This allows advancing the catheter through the inflow rinsing channel of the neuro-endoscope, with only minimal increase in flow resistance. The most suitable dimension was determined within the main boundary conditions: small enough for minimal flow resistance through the flushing channel; large enough to permit accurate dynamic pressure transduction.

❸ Likewise, in the central venous pressure measurement device (chapter IV), polyimide capillaries were selected to permit accurate pressure transduction while minimally interfering with the flow through the main channel of the central venous catheter.

I4.3 Software for development of the algorithms

All algorithms were developed by Alain Kalmar in visual basic software. A particular advantage of this environment is that all algorithms can be first conceived in VBA for excel, which eases visualisation of curves and management of data significantly. Those algorithms were directly transferred to visual basic for ❶ implementation in the stand-alone real-time

software on PC and ❷ integration in the dedicated electronic hand-held device described in chapter II.4.

5

I5 Developed applications

The studies on pressure waveform characteristics in different organ systems, and the subsequent development of prototype devices to implement the gained insights for practical diagnostic purposes led to three different applications:

❶ A hand-held device for the automatic detection of oesophageal intubation in emergency situations.

❷ An improved monitoring technique with a significantly increased accuracy for intracranial pressure measurements during endoscopic neurosurgery.

❸ A device for safe and efficient reversible upgrading of a single lumen central venous catheter to a multilumen catheter with separate channels for accurate pressure monitoring or separate administration of medication.

6

I6 Clinical and scientific results

The studies resulted in the publication of 4 full papers and 4 patent applications:

1. A Novel method to detect accidental oesophageal intubation based on ventilation pressure waveforms.
   Resuscitation 2012; 83: 177– 82.

2. Automatic detection of oesophageal intubation based on ventilation pressure waveforms shows high specificity in patients with pulmonary conditions.
   Resuscitation. 2016; 105: 36-40.

3. Excessive chest compression rate is associated with insufficient compression depth in prehospital cardiac arrest. Resuscitation. 2012; 83: 1319-23.

4. Pressure monitoring during neuroendoscopy: new insights
   Br J Anaesth. 2011 Aug;107(2):218-24.
5. Koen Monsieurs, Alain Kalmar
   Methods and systems for analysing resuscitation. PCT/EP2009/066851
6. Koen Monsieurs, Alain Kalmar
   Methods and systems for ventilating or compressing. PCT - WO2011/154499.
7. Frank Dewaele, Alain Kalmar
   Endoscopic pressure detection assembly. PCT/EP2009/066851
8. Frank Dewaele, Alain Kalmar, Bart Blanckaert, Cyriel Mabilde
   Capillary tube assembly. PCT/EP2011/062810

II

Cardiopulmonary resuscitation & Oesophageal intubation

1

II1 Emergency endotracheal intubation

II1.1 The anatomy of endotracheal intubation

When a patient needs to be mechanically ventilated or the airway needs to be protected against undesirable material such as stomach acid, a cuffed plastic tube must be advanced between the vocal cords into the trachea (windpipe). The entrance of the trachea lies anterior of the neck, requiring the use of a laryngoscope and specific training to visualise the vocal cords and advance the endotracheal tube. Dorsal of the trachea lies the oesophagus. Erroneous oesophageal intubation is one of the main causes of avoidable failed resuscitations.

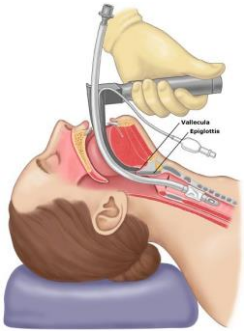


Figure 1: endotracheal intubation
Source: UpToDate

II1.2 Challenges in emergency situations

In the operating theatre, ideal conditions are created for optimal visualisation of the vocal cords. The patient is positioned at a convenient level for visualisation, and the anaesthesiologist, supported by a trained nurse performs the task. In case of difficult visualisation, advanced tools are available such as video laryngoscopy, or fibre bronchoscopy. Subsequently, many additional tools are available to assess the correct location of the endotracheal tube, such as auscultation, waveform capnography or spirometry.

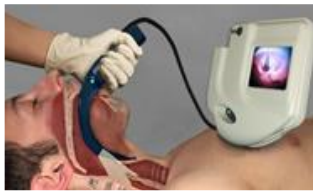


Figure 2: video laryngoscopy.

In emergency situations such as out-of hospital cardiac arrest, acute neurologic syndromes, traffic accidents or disaster medicine, intubation circumstances are much less ideal: patient positioning and lightening circumstances are often extremely inconvenient, and most conventional technologies for subsequent assessment of tube position are unavailable or unreliable, resulting in erroneous intubation, often with fatal outcome. This demonstrates a need for a new method to evaluate endotracheal tube position which is convenient and reliable in such circumstances.

II1.3 Disposable kit for dual endotracheal pressure measurement

After successful endotracheal intubation, synchronous pressure measurement at the distal and proximal end of the endotracheal tube can potentially give clinically valuable information about the quality of chest compressions, of cardiac activity, pulmonary conditions and the location of the endotracheal tube. In order to permit these measurements, we developed a disposable kit which allows easy use in emergency settings, and can at least initially be used for clinical research. If the proof of principle is delivered through the use of this device, a more advance dedicate endotracheal tubes can be envisaged for routine use, where our system is integrated in the endotracheal tube itself.

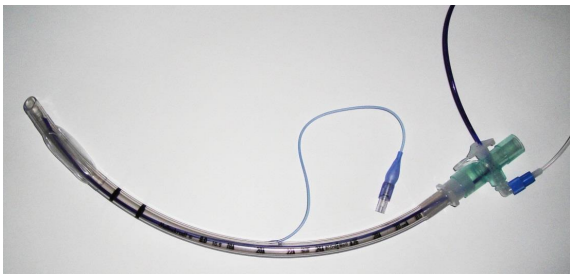


Figure 3: Disposable kit consisting of a semi-rigid catheter with a lumen of one mm that is introduced through the endotracheal tube down to its distal end, with a second catheter connected to the proximal end of the tube.

II1.4 Development of a device for oesophageal intubation detection

The compliance of the trachea/lungs was expected to be radically different from the compliance of the oesophagus/stomach. Therefore we performed test ventilations on intubated pigs, both in the lungs and in the oesophagus and recorded the pressure waveforms in two locations of the endotracheal tube. This revealed a distinct pattern in either tube location. Based on this information, we developed an automated algorithm to quantify these differences, when applied on synchronous pressure readings in the endotracheal tube.

Because the hardware used to detect accidental oesophageal intubation could equally be used for optimising cardiopulmonary resuscitation (CPR), this increases the practical potential of the used methodology. A sequence of studies was performed to develop a pre-commercial prototype and evaluate its validity.

1. In a first study in 40 healthy anaesthetised patients, an algorithm was validated to have a very high sensitivity and specificity to differentiate between oesophageal and tracheal intubation. The disposable kit was introduced in the endotracheal tube and connected to conventional universal disposable pressure sensors. The pressure waveform was registered on the anaesthesia monitor and recorded on a PC for subsequent offline analysis with the dedicated algorithm.
   Resuscitation 2012; 83: 177– 82.

2. As a subsequent step, an electronic handheld device was developed (in cooperation with Prof P. Rombouts) consisting of two-channel device where pressure transducers, signal filters, amplifiers, digitisation, data logger and Bluetooth hardware are integrated. The signal was transmitted to a PC for subsequent data analysis using the same algorithm as the first study. Because the algorithm relies on the difference in the dynamic compliance between pulmonary and gastric system, it was unclear whether the high specificity to confirm tracheal intubation would be preserved in patients with pathologically low pulmonary compliance. Therefore, the new hardware was utilised in a second study to analyse tracheal ventilation pressure profiles in patients on intensive care with very severe pulmonary disease. This study confirmed ❶ the reliability of the hand-held hardware and ❷ the reliability of the algorithm in a patient population with decreased pulmonary compliance.
   Resuscitation. 2016; 105: 36-40.

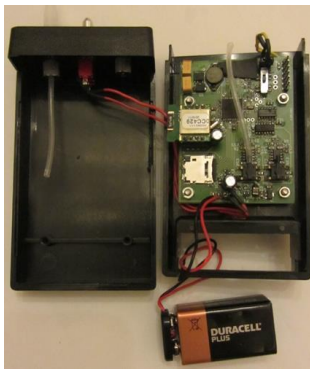


Figure 4: prototype stand-alone device

3. In a third step, a next generation stand-alone device was developed with newer electronics, and integrated algorithms for automatic detection of a ventilation cycle and diagnosis of tube location. A green/red LED was used to communicate the diagnosis. In addition, the algorithm needs to be validated in the appropriate target population, namely prehospital patients. This population is different from anaesthetised patients because of the presence of pneumonia, pulmonary oedema, loss of muscle tone in the oesophagus, and the presence of CPR artefacts on the pressure signal. This clinical validation is an essential step to assure that the technology is robust even in the most challenging patients and working conditions. The new device was used in a clinical evaluation in patients in emergency out-of-hospital resuscitations at Antwerp University Hospital. Data analysis is ongoing.

2

II2 Methods and systems for analysing resuscitation

United States
Patent Application Publication

Pub. No.: US 2011/0245704 A1
Pub. Date: Oct. 6, 2011

Adapted from: "methods and systems for analysing resuscitation"
Date of PCT filing: Dec.10. 2009
Inventors: K Monsieurs, **AF Kalmar**

Abstract

This invention relates to a system generating control signals for compressing or ventilating, respectively. The system comprises a computing device dedicated to process, for a resuscitation, information regarding a compression parameter and/or ventilation parameter, as function of a parameter indicative of blood circulation, a process component for evaluating the different values of the chest compression parameter and/or ventilation parameter as function of the parameter indicative of the blood circulation. The obtained function will generate a value for chest compression parameter and/or the ventilation parameter respectively, and a control signal generator for generating control signals according to the derived ventilation parameter or chest compression parameter.

II2.1 Field of the invention

The present invention relates to a medical device for analysing resuscitation, for example in case of intubation of a patient, or for optimising chest compression depth and ventilation pressure.

II2.2 Background of the invention

When a patient needs positive pressure ventilation or chest compression (resuscitation), a number of clinical issues may arise, such as:

- ***Oesophageal intubation***
  Wrong intubation into the oesophagus, if detected too late, may result in the death of the patient because of a lack of oxygen and ventilation. It is a common problem in emergency situations, both during cardiac arrest and in patients with spontaneous circulation.

- ***Hyperventilation and air trapping during CPR***
  This results in decreased coronary perfusion pressure and in excess mortality in animal studies. Early detection and avoidance of hyperventilation and subsequent increased intrathoracic pressures during resuscitation may be an accurate means for preventing failure of resuscitation and for increasing survival chances and therefore is an important clinical issue.

- ***Assessment of the quality of CPR***
  During resuscitation, several variables, such as chest compression rate and depth, intrathoracic pressure variation, ventilation frequency and pressure should be within certain limits for optimal outcome. Continuous monitoring of these variables allows for optimisation of the resuscitation effort, both in manual and automated resuscitation.

II2.3 Summary of the invention

The present invention demonstrates applications permitting:

1. An accurate detection of the proper position of an endotracheal tube, substantially independent of the person who needs to perform the detection
2. An accurate analysis of resuscitation
3. An accurate and quick detection of spontaneous cardiac activity

II2.4 Schematic description of the diagnostic algorithm

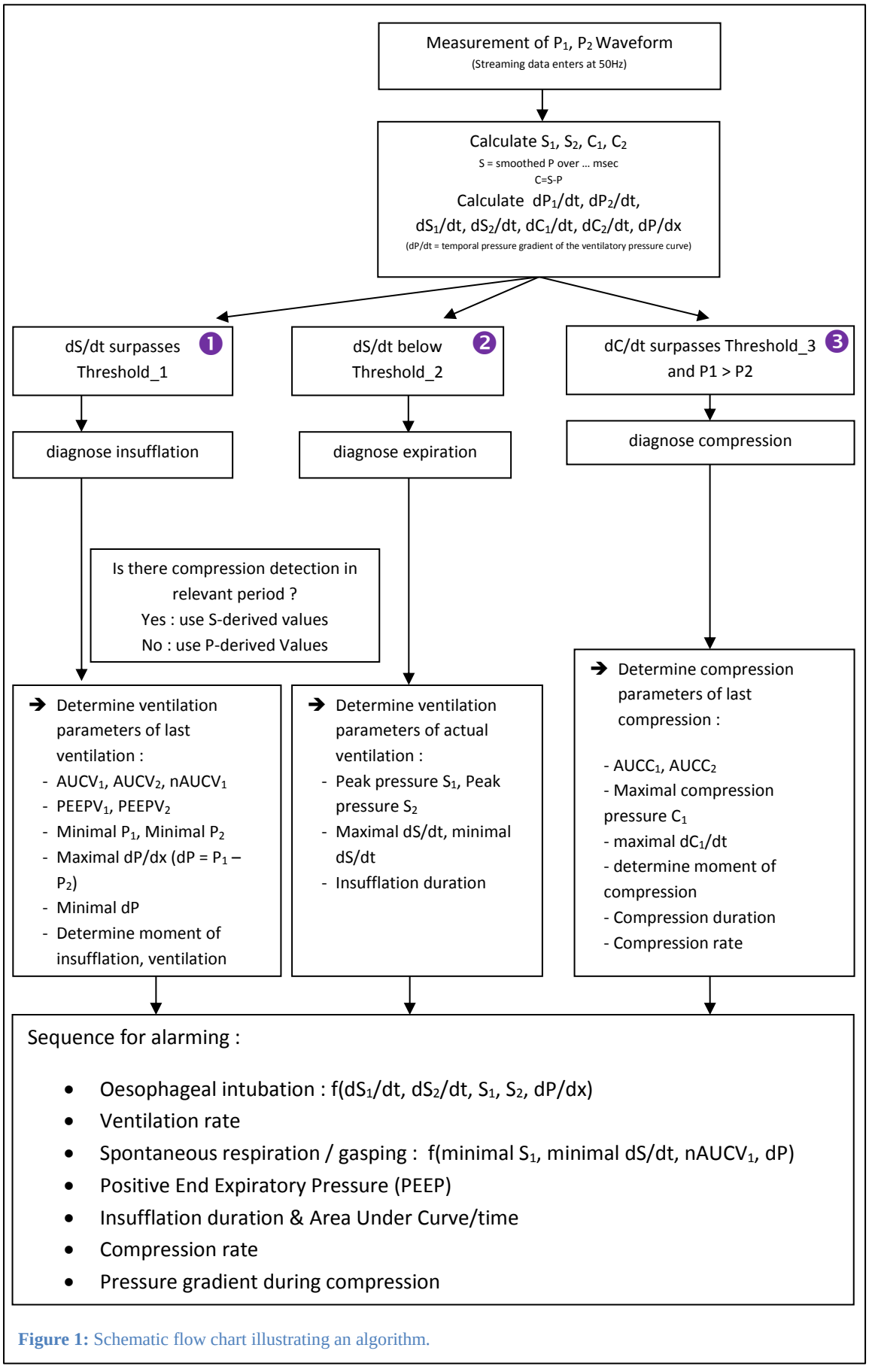


Figure 1: Schematic flow chart illustrating an algorithm.

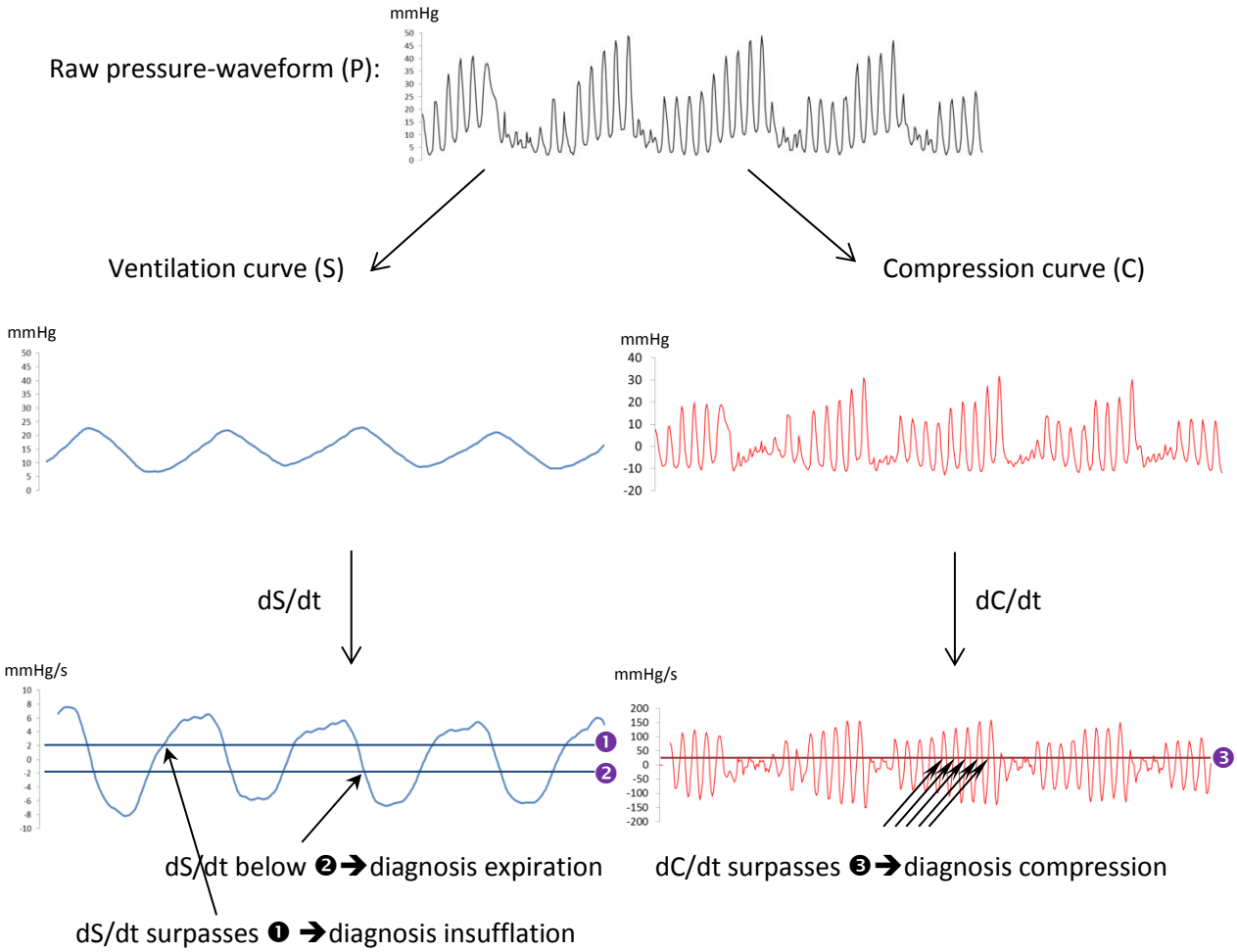


Figure 2: Example of an automatic analysis of the raw pressure recording P_x to extract information on ventilation and compression. This illustrative figure was not part of the patent application. The curve P is a recording at 150Hz of a patient being mechanically ventilated while performing chest compressions. The curve results from a superposition of the effects of ventilation and chest compressions. An averaging algorithm calculates S_x from the pressure curve P_x. The S_x-curve reflects the intrathoracic pressure curve resulting from ventilation as if no chest compressions were performed. Subsequently, the S_x-curve is subtracted from the P_x-curve to calculate the C_x-curve. The C_x-curve reflects the intrathoracic pressure curve resulting from chest compressions as if no ventilation was performed. The C_x-curve looks very similar to the P_x-curve, but the Y-axis demonstrates that the values oscillate around 0 mmHg. The apparent continued presence of ventilatory oscillations are a result of the cyclic negative pressures in the P_x-curve resulting from stronger recoil with subsequent more pronounced negative pressures. In order to operationalize specific events, the first derivative of both the S_1-curve and the C_1-curve is calculated. When the first derivative crosses a certain threshold, a specific event is diagnosed:

- A sharp increase in the S_1-curve (resulting in a high dS/dt value) is a result of insufflation of air.
  → when dS/dt increases above a threshold value ❶, insufflation is diagnosed.

- A sharp decrease in the S_1-curve (resulting in a deep negative dS/dt value) is a result of expiration of air.
  → when dS/dt drops below threshold value ❷, expiration is diagnosed.

- A sharp increase in the C_1-curve (resulting in a high dC/dt value) is a result of chest compression.
  → when dC/dt increases above threshold value ❸, chest compression is diagnosed.

II2.5. Clinical decision making

Further automated analysis of the pressure signals and their derivatives, may help in the clinical decision making regarding:

- **Oesophageal intubation detection**
  The difference in compliance between the lungs and the oesophagus results in very significant differences in the characteristics of :
  1. the pressure gradient over time of the endotracheal pressures (dP/dt)
  2. the pressure gradient between two different measuring points at a given time (ΔP).

  Using the pressure curves obtained during the initial ventilation cycles, e.g. during the first four ventilation cycles, quick distinction can be made between the tracheal and oesophageal pressure patterns. This information will allow the health care provider to establish correct intubation or to remove and replace the tube.

- **Assessment of chest compression and compression rate**
  The pressure gradient (dP/dt) may be used for determining the onset and release of chest compressions, and further determination of the quality of the chest compression rate and the resulting intrathoracic pressures variations.

- **Assessment of return of spontaneous circulation**
  Spontaneous circulation may be evaluated based on a pulse pressure. The combination of pulse pressure, identified as the maximal pressure difference in between a sequence of a negative dP/dt followed by a positive and subsequently negative dP/dt, may allow confirmation of spontaneous circulation with higher sensitivity/specificity.

- **Assessment of ventilation variables**
  Ventilation variables such as **ventilation cycle**, **ventilation frequency**, the fraction of the time during which the **ventilatory pressure** is higher than a certain value, **presence of PEEP** (Positive End-Expiratory Pressure) and **return of spontaneous respiration**.

II2.6 Integration of pressure values with other parameters

In order to further improve the information obtained with the system, information from endotracheal pressure analysis can be integrated with other parameters to improve the sensitivity/specificity of automatic diagnostic algorithms. For example, appearance of a peak in the intrathoracic pressure systematically following the R-wave on an ECG indicates a higher probability of the presence of a true spontaneous cardiac compression than conclusions drawn when the ECG-information is absent.

II2.7 Further reading

See appendix 1 for a more detailed description of the patent

3

II3 A novel method to detect accidental oesophageal intubation based on ventilation pressure waveforms

Resuscitation 2012 Feb; 83: 177– 82.

Kalmar AF, Absalom A, Monsieurs KG.

II3.1 Abstract

Background: Emergency endotracheal intubation results in accidental oesophageal intubation in up to 17% of patients. This is frequently undetected thereby adding to the morbidity and mortality. No current method to detect accidental oesophageal intubation in an emergency setting is both highly sensitive and specific. We hypothesized that, based on differences between the mechanical properties of the oesophagus and the trachea/lung, ventilation pressures could discriminate between tracheal and oesophageal intubation. Such a technique would potentially not suffer some of the limitations of current methods to detect oesophageal intubation in emergency conditions such as noisy environment (making clinical assessment difficult) or low/no flow states (reducing the applicability of capnometry). The aim of our study was thus to develop and assess a technique that may more rapidly and accurately differentiate oesophageal from tracheal intubation based on airway pressure gradients.

Materials and methods: Forty adult patients undergoing elective surgery were included. In 20 patients the trachea was intubated with an endotracheal tube; in 20 patients the oesophagus was purposefully intubated using an Easytube® (Rüsh, Germany). In all patients, a thin air-filled catheter was inserted through the tube lumen until its tip was 1 cm from the distal end, and connected to a pressure transducer. Pressure was recorded simultaneously from a second catheter at the proximal end of the tube. For the first three manual ventilations in each patient,

a parameter (D) based on temporal (ΔP/Δt) and spatial (ΔP) pressure gradients (and reflecting flow divided by elastance) was calculated and evaluated for its ability to discriminate between oesophageal and tracheal intubation.

Results and discussion: For all tracheal ventilations, D-values were >0.5 (range 0.6–47.9), while for all oesophageal ventilations D-values were <0.5 (range 0.0005–0.07).

Conclusion: This technique has the potential to provide a diagnosis of failed intubation within seconds with high sensitivity and specificity.

II3.2 Introduction

In the elective operating theatre, accidental oesophageal placement of an endotracheal tube is not uncommon, but is usually detected by a combination of clinical assessment, spirometry and capnography. Moreover, in this setting, the lungs are usually adequately preoxygenated, which substantially increases the apnoea time before the onset of hypoxia and limits the risk of hypoxic injury.

In emergency situations, the incidence of accidental oesophageal intubation is higher, not only in patients undergoing cardiopulmonary resuscitation, but also in patients with spontaneous circulation, such as in patients with severe neurotrauma or acute respiratory failure. In these situations, which mostly occur in the pre-hospital setting, intubation is commonly performed by personnel with less experience of intubation (than practicing anaesthetists), under conditions that are far from optimal. These factors contribute to an unrecognized oesophageal intubation rate of up to 17%, which adds significantly to the morbidity and mortality of these patients.[1–3] Apart from causing hypoxia and hypercapnia, oesophageal ventilation causes gaseous distension of the stomach, which will hinder tracheal ventilation even after successful subsequent intubation and cause a risk of regurgitation and pulmonary aspiration in these (often non-fasted) patients.[4]

In the absence of direct vocal cord visualization (which is not always possible during emergency intubation), the most widely used methods of confirming tracheal intubation are clinical assessment (observation of chest movement and auscultation of the chest and epigastrium) and the use of end-tidal carbon dioxide monitoring[5] (waveform, color change or digital readout). However, the latter technique cannot always confirm an appropriately placed tube, since chest compressions do not always generate sufficient blood flow to provide an end-tidal carbon dioxide measurement. Moreover, mouth-to-mouth resuscitation before intubation or the presence of carbonated beverages in the stomach may cause false positive carbon dioxide readings after oesophageal intubation.[6] Several newer methods have been developed to detect misplaced tubes. These include acoustic methods (such as automated analysis of lung auscultation,[7] vibration[8] or reflectometry[9]), ultrasound performed at the suprasternal notch,[10,11] the use of an oesophageal detector device[12] (assessment of the suction of air through the tube by means of a self-inflating bulb or a syringe) and chest impedance

measurements.[13] Léon et al.[14,15] used a combination of proximal pressure and spirometry readings to propose a diagnostic oesophageal detection device using neural network technology. More recently, analysis of pressure–volume relationships of the endotracheal tube cuff was shown to be useful in detecting oesophageal intubation in pigs.[16] All show some promise but either lack practicality or have insufficient sensitivity and specificity, especially during cardiac arrest.[17] An oesophageal detector device is sensitive for detecting misplaced tubes, but lacks specificity and if relied upon, will result in removal of about 30% of correctly placed tubes in cardiac arrest patients.[18] Chest impedance measurements from surface electrodes appear to be highly sensitive and specific, but are impractical since they are only valid in stable conditions where the electrodes are first carefully applied at specific locations and calibrated in a spontaneously breathing patient before endotracheal intubation.[13,19]

There is therefore a clinical need for a device that is small enough to be practical in emergency situations and that can detect oesophageal intubation within seconds, even in the absence of cardiac output. We hypothesized that, based on differences between the mechanical properties of the oesophagus and the trachea/lung, ventilation pressures could discriminate between tracheal and oesophageal intubation. Thus, in the current study we investigated if analysis of temporal and spatial pressure gradients within the endotracheal tube can reliably differentiate between oesophageal and endotracheal intubation.

II3.3 Methods

After approval by the Ethics Committee of the University Medical Center Groningen, written informed consent was obtained from 40 consecutive adult patients. Exclusion criteria were: known oesophageal pathology, expected difficult oral intubation, American Society of Anesthesiology (ASA) status > II, age <18 or >75 years.

The first group consisted of 20 patients scheduled for a surgical procedure under general anaesthesia and requiring tracheal intubation. Upon arrival in the operating theatre, standard monitoring was applied: ECG, pulse oximetry and non-invasive automated arterial blood pressure. For induction of anaesthesia, a syringe pump with propofol 6 mg/kg/h was started, anaesthesia was induced with propofol (1–2 mg/kg) and sufentanil (0.25 g/kg) and cisatracurium (0.15 mg/kg) were administered. Anaesthesia was maintained with propofol and the trachea was intubated with an endotracheal tube (Lo-Contour™, Mallinckrodt, Hazelwood, MO, USA). The length of the endotracheal tube was 32 cm, the internal diameter was 8 mm. After securing the airway, an adapted straight 7.6 mm connector (type 1947, Intersurgical®, Berkshire, UK) was connected to the proximal end of the endotracheal tube. Via this connecting piece (Fig. 1), a thin polyethylene disposable air-filled catheter (Vygon 71100.20, Ecouen, France) with an internal diameter of 1 mm was introduced in the tube, positioned at 1 cm from its distal end and connected to a pressure transducer (Truwave PX-600F, Edwards Lifesciences LLC, Irvine, CA, USA) via a luer-lock connection. A second air-filled catheter was attached at the connecting piece itself and connected to a second pressure

transducer. Both systems were calibrated against atmospheric pressure and both pressure transducers were connected to a Philips IntelliVue MP70 monitor (Philips Medizinsysteme, Boeblingen, Germany) and linked to a portable computer. The trachea was manually ventilated three times as in normal test ventilations after intubation with a 2 l ventilation bag (type 2820, Intersurgical®, Berkshire, UK). The pressure waveforms were sampled at 50 Hz and recorded using Rugloop II data-manager software (Demed, Temse, Belgium).

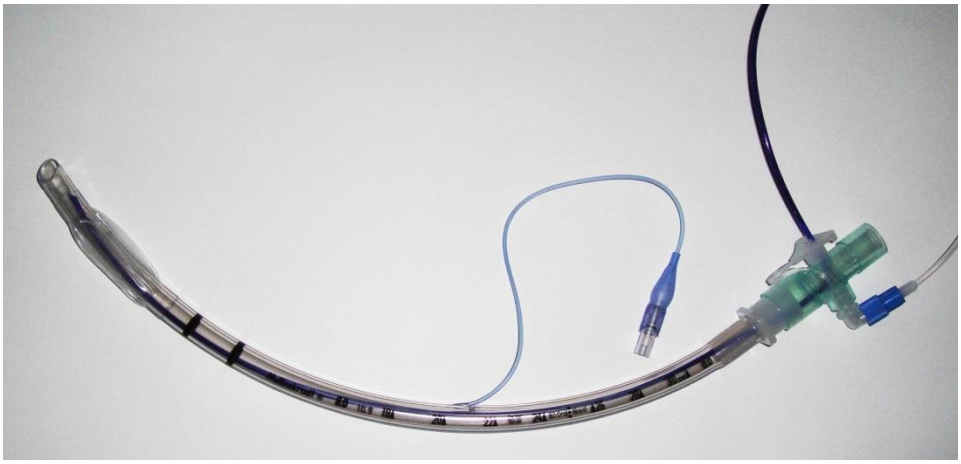


Figure 1: Endotracheal tube with connecting piece and two air-filled catheters. The proximal catheter is attached to the connecting piece, the distal (painted blue) enters the connecting piece and is inserted into the endotracheal tube.

In the second group, 20 other consecutive patients scheduled for a surgical procedure under general anaesthesia, but not requiring tracheal intubation, were also included. These patients were given the same anaesthetic regimen. To simulate accidental oesophageal intubation but at the same time allowing secure ventilation of the lungs, the oesophagus was intubated under direct laryngoscopy using a 41 Fr Easytube® double lumen Airway (Teleflex Medical, NC, USA) and both cuffs were inflated. The Easytube® is a supraglottic airway device consisting of a double-lumen tube with one lumen ending more distally than the other. During positioning of the Easytube® (blindly when used routinely) the distal end is either located in the oesophagus or in the trachea while the more proximal lumen ends in the pharynx. After inflation of the proximal and distal cuffs, a free airway and protection against aspiration are achieved. The length of the oesophageal lumen of the Easytube® was 31 cm; the internal diameter was 8 mm. Then, the oesophageal lumen of the Easytube® was manually ventilated three times with a 2 l ventilation bag (type 2820, Intersurgical®, Berkshire, UK) and the pressure waveforms were recorded as described previously. These manual ventilations were performed simulating normal test ventilations after intubation. Special care was taken to perform the ventilations similarly in the oesophageal group and in the tracheal group.

II3.3.1 Data analysis

In subsequent offline analysis, the pressure data were converted to ASCII format and imported into Microsoft Excel. Custom developed Visual Basic for Applications (VBA)

software (written by A. Kalmar) was used for visualization and analysis of the ventilation pressure waveforms.

During the insufflation portion of a manual ventilation cycle, very different pressure/volume relationships for the trachea and oesophagus can be expected because of differences in compliance, a valve-like effect of the oesophagus wall on the orifice of the tube, and sudden opening of the lower oesophageal sphincter (LOS). As a result, during oesophageal insufflation, the distal tube pressure will rise at a higher rate, while the pressure gradient from the proximal to the distal end of the tube will be lower (Fig. 2).

II3.3.1.1 Analysis of pressures during insufflation (parameter 1)

First, for every ventilation cycle, we analyzed the inspiratory waveform, to identify the time at which the maximum increase in distal tube pressure ($\Delta P_{dist}/\Delta t$ with Δt = 300 ms) occurred (Fig. 2, γ). The proximal and distal pressures at that time point were then determined, and used to calculate the spatial pressure difference along the tube (ΔP). Finally, we calculated a parameter 1, which correlates inversely with the maximal compliance, reflecting elastance as follows: $E = \frac{dP_{dist}/dt}{\Delta P} \times P_{dist}$, at the moment of maximal dP_{dist}/dt.

II3.3.1.2 Cumulative pressure gradients during expiration (parameter 2)

Because we considered that the exhaled volume of air would be significantly less after oesophageal ventilation compared to tracheal ventilation, we developed a second parameter that correlates with expiratory flow and volume.

The start of the exhalation period (α, see Fig. 2) was defined as the moment within the ventilation cycle after the occurrence of distal peak pressure when the distal pressure becomes higher than the proximal pressure. The end of the exhalation time (β, see Fig. 2) was arbitrarily determined as 2 s later. Over the interval [α − β], the cumulative absolute difference was determined as $\Sigma \Delta P/\Delta x = \sum_{\alpha}^{\beta} \left| P_{dist} - P_{prox} \right|$ (grey area in Fig. 2).

The mechanical meaning of this parameter is the flow through the tube (since only flow can cause a pressure difference) during exhalation. As the lungs are much better equipped to accept and return the air volume, the value of this parameter will be much higher in tracheal than in oesophageal ventilation.

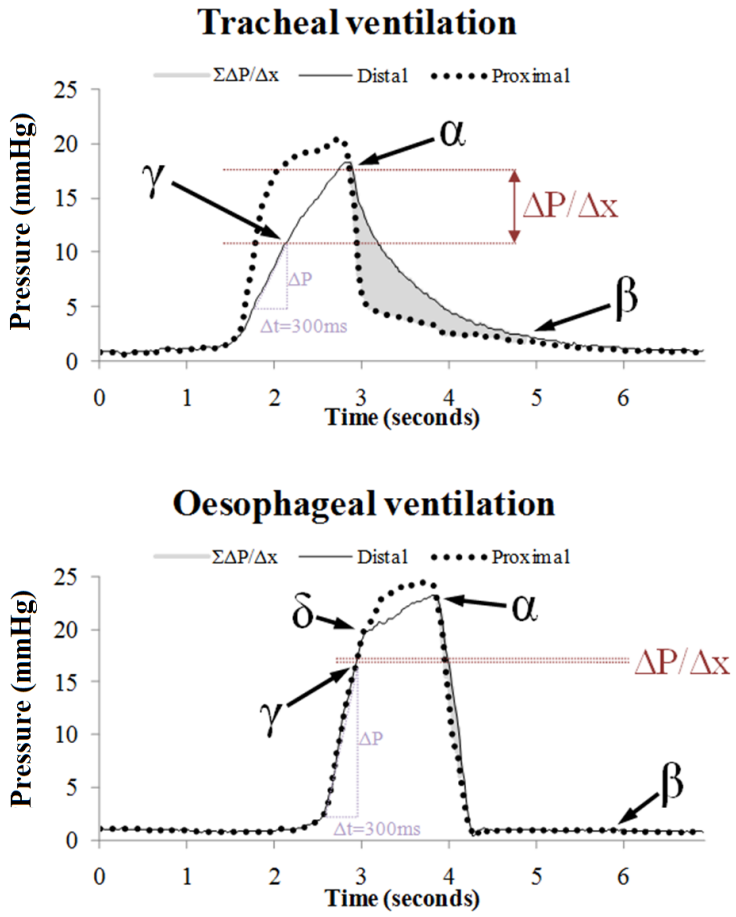


Figure 2: Examples of distal and proximal pressure waveforms recorded in the trachea and oesophagus. At the beginning of oesophageal insufflation, the lumen of the oesophagus is being filled with air with very small pressure increase. Once the oesophageal lumen is filled, there is a very fast increase in wall stress and consequently a fast increase in pressure (γ) at low flow. When the ventilation pressure overcomes the lower oesophageal sphincter pressure (δ) the increase in pressure is less steep and there is a fast increase in flow. During exhalation, there is a steep decrease in distal pressure. The point at which the distal ventilation pressure becomes lower than the proximal pressure is defined α. 2 s later is defined β. The grey area reflects ΣΔP.

II3.3.1.3 Parameter 3

Thirdly, for every ventilation cycle, a D-value was determined as the ΣΔP-value divided by the E-value. As such, the D-value represents flow divided by elastance. In addition, the proximal peak pressure (PP_{prox}) was determined as a measure of ventilation force.

II3.3.2 Statistical analysis

Based on pilot measurements in pigs (not published), a high sensitivity and specificity was expected. Therefore a sample size of 20 patients in each group was considered appropriate. Statistical analysis was performed using SigmaPlot V10.0 (Systat software©, CA, USA).

The Chi-square test, the Student's t-test and the Fisher's exact test were used to determine statistical differences between groups for demographic variables. A P-value <0.05 was considered significant. Results are presented as median (25^{th}–75^{th} percentile) and range.

Within-group differences among first, second and third ventilations were tested using the two-tailed Student's t-test for paired observations. These tests were performed for E-values, ΣΔP-values and for PP_{prox}. Between-group differences were tested using the two-tailed Student's t-test for unpaired observations. .

II3.4 Results

	Tracheal	Oesophageal	P-value
Female/Male	6/14	13/7	0.016
Age (yrs)	61 (20-81)	51 (20-80)	0.15
Weight (kg)	76 (60-109)	77 (60-103)	0.43
Length (cm)	175 (160-192)	175 (158-190)	0.90
Body Mass Index (kg m^{-2})	25 (20-31)	25 (20-35)	0.63

Table 1: Demographic data of patients included in the oesophageal and tracheal groups. Values are presented as proportions or median (range).

Table 1 shows the demographic data of the patients in both groups. None of the patients showed any signs of oesophageal discomfort in the postoperative period and all patients could leave the post-anaesthesia care unit within a normal period. Fig. 2 shows typical distal and proximal pressure waveforms of tracheal and oesophageal ventilations respectively.

Sixty tracheal and 58 oesophageal ventilations were recorded. In two patients, there was an inadvertent recording of only two oesophageal ventilations. Fig. 3 shows the individual E-values, ΣΔP-values and D-values calculated from the tracheal ventilations (left) and from the oesophageal ventilations (right). Minimum, lower quartile, median, upper quartile and maximum values are summarized in Table 2.

		Min	25^{th}	Median	75^{th}	Max
E-Value	**Tracheal**	6	15	23	45	177
	Oesophageal	443	1011	1407	1841	3037
ΣΔP	**Tracheal**	70	180	246	294	571
	Oesophageal	1	2	6	14	56
D-Value	**Tracheal**	0.6	4.3	10.2	16.1	47.9
	Oesophageal	0.0005	0.0016	0.0041	0.0102	0.0751

Table 2: Lowest value, 25th percentile, median value, 75th percentile and highest value of the calculated discriminative parameters in tracheal (n=60) and oesophageal (n=58) ventilations.

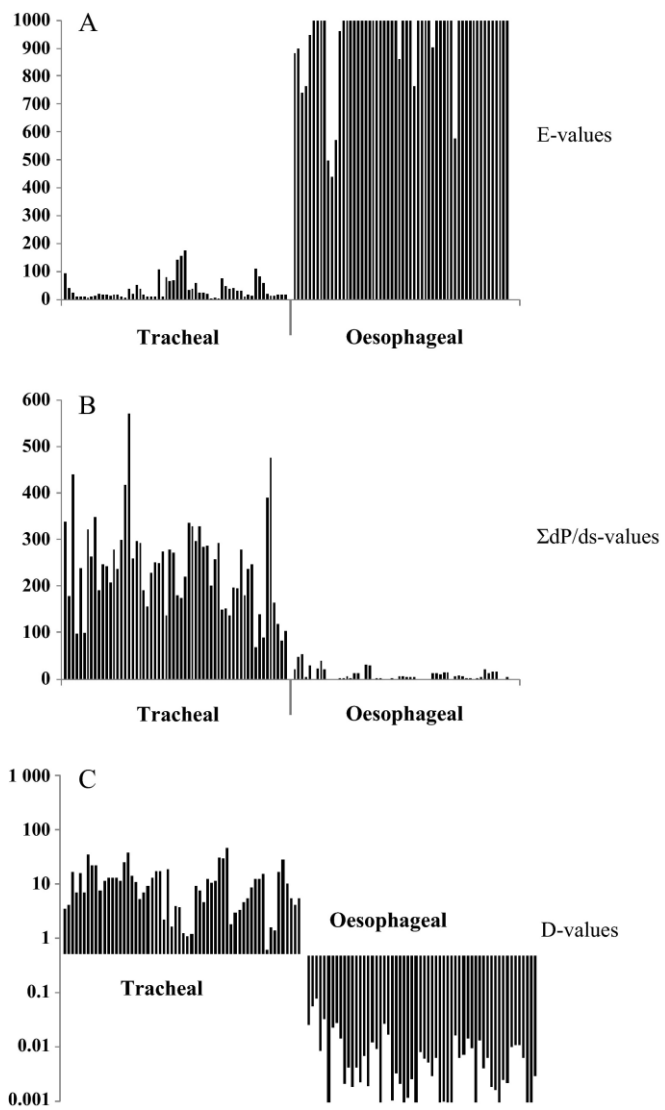


Figure 3: E-values (A), ΣΔP (B) and D-values (C) recorded from 20 patients in the trachea (left) and from 20 patients in the oesophagus (right). A and B are represented on a linear scale, C is represented on a logarithmic scale.

Figure 4 shows box-plots of the E-values for the first, second and third ventilations in the tracheal and oesophageal groups respectively. In the tracheal ventilations, median E-values of the first, second and third ventilations were 23, 24 and 22 respectively. The E-values in the second (P = 0.86) and third (P = 0.49) tracheal ventilations were not significantly different from the first ventilation. Median PPprox of the first, second and third ventilations were 20, 21 and 20 cm H_2O respectively. The PPprox in the second (P = 0.11) and third (P = 0.13) tracheal ventilations were not significantly different from the first ventilation. In the oesophageal group, median E-values of the first, second and third ventilations were 1055, 1604 and 1679 respectively.

The E-values of the second (P = 0.004) and third (P < 0.001) oesophageal ventilations were significantly different from the first ventilation.

Median PPprox of the first, second and third ventilations were 24, 26 and 25 cm H_2O respectively. The PPprox in the second (P = 0.01) and third (P = 0.002) oesophageal ventilations were statistically different from the first ventilation. E-values between tracheal and oesophageal ventilations differed significantly (P < 0.001). The median (IQR) distal pressures (P_{dist}) at the moment of maximal dP_{dist}/dt were 22 (20–25) cm H_2O in the oesophageal measurement and 9 (7–11) cm H_2O in the tracheal measurements.

In the tracheal as well as the oesophageal group, there were no significantly different results among the first, second and third ventilations for ΣΔP-values and D-values. A threshold value of 0.5 for the D-value was 100% sensitive and specific for tracheal intubation in the patients we studied.

II3.5 Discussion

In patients undergoing elective intubation in the operating theatre, parameters reflecting flow and elastance, calculated from analysis of pressure profiles in the endotracheal tube, were able to discriminate between tracheal and oesophageal intubation in all cases. This result is based on the different mechanical properties of the trachea/lung system and the oesophagus.

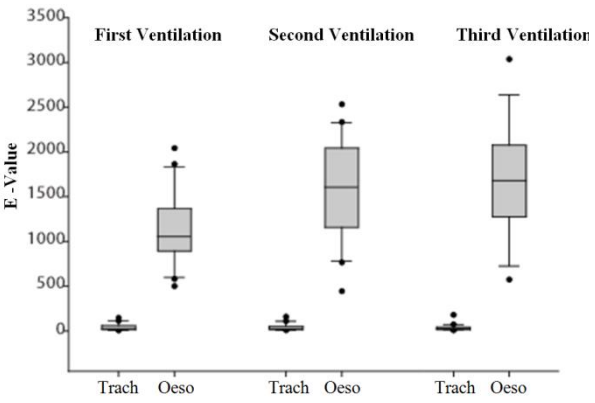


Figure 4: Box plots of E-values for the first, second and third ventilations in the tracheal and oesophageal groups. The E-values of the second (P = 0.004) and third (P < 0.001) oesophageal ventilations were significantly different from the first ventilation.

During insufflation of the oesophagus, a very steep increase in distal pressure (and consequently a high dP_{dist}/dt) is seen at the moment where there is not yet significant flow (this is before opening of the LOS). Any ventilation will always cause a significant volume flow of air, but in case of oesophageal insufflation, this volume will only be insufflated after opening of the LOS. This is reflected in a sudden divergence of the distal and proximal pressure curves (Fig. 2, δ). Consequently, at the moment of maximal dP_{dist}/dt (Fig. 2, γ), there is a very low ΔP. On the other hand, during tracheal ventilation, because of the much higher compliance of the lungs, the maximal dP_{dist}/dt is reached at high flows, resulting in a relatively much lower E-value.

Although median PPprox of consecutive oesophageal (but not tracheal) ventilations varied somewhat, we judged these differences to be clinically insignificant. Figure 4 shows that no significant differences in E-values were found between consecutive tracheal ventilations, but highly significant differences were found between consecutive oesophageal ventilations. This is probably a consequence from changing compliance caused by earlier gastric insufflations.

As can be visually appreciated in figure 2, the difference in pressure between the proximal and distal pressure curves in the period between points ¸ and ˇ is much higher in tracheal than in oesophageal insufflations. Both the E-value and the ΣΔP-value represent different aspects of the response to ventilation of trachea and oesophagus. Therefore, an integration of these two parameters resulted in a parameter with even more discriminative power, as shown in figure 3C where the ratio of the ΣΔP-value and the E-value results in the discriminating D-value. Every tracheal ventilation resulted in a D-value higher than 0.5, and every oesophageal ventilation resulted in a D-value lower than 0.5. Moreover, the lowest tracheal D-value was eight times higher than the highest oesophageal D-value.

The proposed method uses a distal catheter in the endotracheal tube. Because using only a proximal pressure measurement would be more convenient, we have also analyzed ventilation pressure characteristics based on the proximal measurements only.

However, while clear correlations between proximal pressure characteristics and the oesophageal/tracheal location were found, no reliable discriminating criteria could be established using only proximal pressure readings. As can be visually appreciated in figure 2, the waveform characteristics of the proximal pressure measurement in oesophageal and tracheal insufflation are not dramatically different, while the distal waveforms do have distinctly different features. These systematic dissimilarities, combined with a flow-related parameter are in our opinion essential for a highly discriminative parameter. The technique developed by Léon et al.[14,15] was tested using mechanical ventilation only and was based on the combination of two distinct techniques (spirometry and pressure measurements) which is an important limitation for its clinical application.

There are some limitations to this study. We performed ventilations manually as during normal practice, but we have not measured ventilation volume and the rescuer was not blinded for the position of the tube. This may have introduced a bias towards more careful ventilations in the oesophagus. However, because parameter E is determined at the moment of maximal ΔP, it is unlikely that smaller ventilation volumes have a significant effect on the performance of the algorithm. Moreover, ΣΔP is determined during exhalation and reflects the exhaled volume of air which is probably less after oesophageal insufflation compared to tracheal ventilation.

Secondly, our study was performed under controlled conditions, with patient characteristics different from emergency patients. Our patients were fasted, they were not ventilated before intubation, they had no apparent lung disease and they were paralyzed using cisatracurium. Further research should elucidate if the algorithm remains accurate in patients with acute or chronic lung disease or in patients that are not completely paralyzed. Since low D-values (<0.5) would indicate a system with poor compliance, such result should be interpreted as either oesophageal intubation or extremely low-compliant lungs. Our observation that the sensitivity remains optimal for subsequent oesophageal ventilations suggests that gastric insufflation prior to the test ventilation (occurring frequently in emergency situations) may not decrease the reliability of the algorithm.

Thirdly, different tubes were used in the tracheal and oesophageal intubation groups. While the diameter of the Easytube® was identical to the diameter of the endotracheal tube, the Easytube® was slightly longer. In case this difference would have influenced the calculated parameters of oesophageal insufflation, oesophageal pressure profiles using an endotracheal tube would have made the differences in the calculated discriminative parameters even larger. This is because a shorter oesophageal tube would make the spatial pressure gradients during oesophageal insufflation even lower, which would if anything, amplify the difference.

Finally, the contribution of the LOS to the increase in pressure in the oesophagus during insufflation of air is not known. In stable haemodynamic conditions, the LOS opening pressure is about 20 cmH_20. Both in pigs and in humans, LOS pressure is reduced during low perfusion conditions such as shock and cardiac arrest.[20,21] Propofol, sufentanil and

cisatracurium do not influence the LOS pressure.[22,23] It remains possible, though, that calculated D-values will be less discriminative in patients with impaired LOS function.

Further studies are required to confirm the applicability of this new technique in patients with reduced LOS opening pressure, and to compare it with current methods such as end-tidal CO2 measurement.

II3.6 Conclusion

In patients undergoing elective intubation in the operating theatre, analysis of ventilation pressure profiles using manual ventilation discriminated between tracheal and oesophageal intubation with high sensitivity and specificity. The advantage of this method is that it can be incorporated into a rapid, real-time automated diagnostic algorithm. Future studies should confirm the efficacy in patients with lung disease and with impaired circulation such as shock or during cardiac arrest.

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4

II4 Automatic detection of oesophageal intubation based on ventilation pressure waveforms shows high specificity in patients with pulmonary conditions.

Adapted from : Resuscitation. 2016; 105: 36-40.

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II4.1 Abstract

Background: Unrecognized endotracheal tube misplacement in emergency intubations has a reported incidence of up to 17%. Current detection methods have many limitations restricting their reliability and availability in these circumstances.

There is therefore a clinical need for a device that is small enough to be practical in emergency situations and that can detect oesophageal intubation within seconds. In a first reported evaluation, we demonstrated an algorithm based on pressure waveform analysis, able to determine tube location with high reliability in healthy patients.

The aim of this study was to validate the specificity of the algorithm in patients with abnormal pulmonary compliance, and to demonstrate the reliability of a newly developed small device that incorporates the technology.

Materials and methods: Intubated patients with mild to moderate lung injury, admitted to intensive care were included in the study. The device was connected to the endotracheal tube,

and three test ventilations were performed in each patient. All diagnostic data were recorded on PC for subsequent specificity/sensitivity analysis.

Results and discussion: A total of 105 values in 35 patients with lung injury were analysed. With the threshold D-value of 0.1, the system showed a 100% sensitivity and specificity to diagnose tube location.

Conclusion: The algorithm retained its specificity in patients with decreased pulmonary compliance. We also demonstrated the feasibility to integrate sensors and diagnostic hardware in a small, portable hand-held device for convenient use in emergency situations.

II4.2 Introduction

Unrecognised misplacement of the endotracheal tube (ETT) during endotracheal intubation and ventilation, has a reported incidence of 2.9% - 16.7% and is a frequent cause of morbidity and mortality in emergency intubations.[1,2,3] In optimal conditions, such as in the operation room during elective surgery, correct positioning of the tube is simple in most cases, and correct tube position can be ensured by using techniques aiming to improve tube placement (such as direct visualisation of the vocal cords) and by techniques to check the position of the tube after placement (such as observation of chest expansion, chest auscultation, capnography, spirometry or more advanced methods such as ultrasound[4] or flexible bronchoscopy). Each of these methods has limitations and is often less reliable or even impractical in the emergency setting, and require significant training for proper interpretation. Capnography with interpretation of the characteristic CO_2 waveform and the $EtCO_2$ value is currently the most reliable method to assess tracheal intubation, with a very high sensitivity and specificity both approaching 100%, although the specificity drops to 70% - 88% in patients with cardiac arrest.[5] Moreover, during cardiopulmonary resuscitation many of these methods require interruption of chest compressions.[6,7] In airborne emergency teams, weight constraints form an additional limitation.

During endotracheal intubation in an acute setting, for example during out-of-hospital cardiopulmonary resuscitation (CPR) or management of facial trauma victims, the risk of oesophageal intubation is substantially increased compared to the controlled operating room setting. Sub-optimal working conditions and the presence of medical personnel less experienced in endotracheal intubation may contribute to an increased risk of oesophageal intubation. In addition limited monitoring and the urgency of the situation may contribute to delayed detection of a misplaced tube. In the acute setting, up to 17% of endotracheal tubes (ETTs) are positioned in the oesophagus, despite the performed checks.[3,8] Unrecognised oesophageal intubation leads to hypoxia and hypercapnia, causing brain damage and eventually death. Even when detected in a timely manner, oesophageal intubation can increase the difficulty of correct re-intubation and increase morbidity and mortality due to aspiration.[9,10]

Chest auscultation is the most commonly used method to confirm ETT placement, but as mentioned it usually requires interruption of chest compressions during CPR.[5,6] In the 2015 European Resuscitation Council (ERC) Guidelines for resuscitation, quantitative waveform capnography is recommended as the standard for confirming correct ETT placement.[11] Well-known limitations of capnography in cardiac arrest victims exist however, as the capnography signal may be falsely low as a result of low cardiac output, low pulmonary flow, airway obstruction, or epinephrine use.[12,13]

Consequently, in order to decrease the incidence of unrecognised oesophageal intubation, there is a need for a diagnostic device that is reliable, very easy to interpret, ultra-portable, economic and preferably integrable in existing devices, providing automatic immediate diagnosis after intubation from the first ventilation onwards. In addition such a device should involve minimal interruption of CPR, be independent of cardiac output, and practical in demanding out-of-hospital circumstances and suboptimal working conditions.

Because pressure sensors are reliable, reproducible, durable, very small, require very low power consumption and calibration, and can measure from a distance through low-cost pressure catheters, a device based on pressure readings could potentially fulfil all the above mentioned requirements.

As shown and quantified in our previous research, the distinct difference in compliance between the trachea/lungs versus the oesophagus/stomach can be exploited to determine misplacement of the ETT. In a first study on two cohorts of 20 healthy patients enrolled for elective surgery, this method could discriminate between oesophageal and tracheal intubation with 100% sensitivity and 100% specificity[14], based on pressure measurements in the ETT recorded through conventional pressure gauges on an anaesthesia monitor, with subsequent offline data-analysis on a PC. The advantage of this new method, compared to the currently available methods, is that it is potentially conclusive after just one ventilation with a very high sensitivity and specificity.

In short, the algorithm calculates a measure of elastance (E-value) during the insufflation phase, and a measure of dynamic compliance ($\sum$-value) during the expiration phase. A discriminative D-value is calculated, as $D = \frac{\sum}{\mathrm{E}}$. Tracheal ventilations typically result in higher D-values (because of a high dynamic compliance during expiration and low elastance during insufflation), whereas oesophageal ventilations result in lower D-values.

In the first reported evaluation[14], our algorithm was assessed using pressure waveforms collected from patients with American Society of Anesthesiology (ASA) physical status I or II. This implies that the study population had healthy lungs with a normal compliance. Many patients requiring emergency intubation, however, may not fit these criteria. In patients with severe obstructive or restrictive pulmonary disease, lung compliance differs significantly from that found in healthy lungs.[15] Since particularly in those circumstances it is essential for the algorithm to preserve its reliability, we performed a second study to evaluate our method in a

more demanding patient population with decreased pulmonary compliance, caused by problems such as acute respiratory distress syndrome (ARDS).

Because of the lower compliance of the lungs in those pathological conditions, and considering the physiological principle on which the algorithm is based, we anticipated that the algorithm might misdiagnose tracheal for oesophageal intubation, and consequently have a lower specificity in this population. Therefore, the aim of the study was to validate the specificity of the algorithm in patients with abnormal pulmonary compliance, admitted to an intensive care unit (ICU).

A secondary aim was to demonstrate the reliability of a newly developed small device that incorporates the technology and algorithm mentioned above. The hand-held device can be connected to an ETT and has integrated pressure sensors and electronics, enabling real-time analysis of the pressure waveforms and immediate alerts in the case of malpositioning of the endotracheal tube. For this research setting, the pressure waveforms are also transmitted through a Bluetooth connection to a laptop for data analysis and display of the waveform.

II4.3. Methods

II4.3.1. Study design and setting

After approval by the Ethics Committee of the University Medical Centre Groningen, a convenience sample of patients in the intensive care unit were included. Inclusion criteria were controlled mechanical ventilation and at least mild to moderate lung injury. To quantify the severity of the pulmonary disease, a Murray score was calculated for each patient[16]. The Murray score is calculated based on alveolar consolidation on chest radiography, PaO_2/FiO_2 ratio, Positive End-Expiratory Pressure (PEEP) and lung compliance. Exclusion criteria were: colonisation with multi-resistant bacteria, possible adverse effects on the patient (the decision was left to the treating physician of the ICU), pregnancy and age < 18 years.

II4.3.2. Study protocol and data collection

In the current study, only tracheal pressure waveforms were recorded. To record the waveforms, a connecting piece was attached to the in-site tube, as described previously.[13] This connecting piece comprised one disposable thin air filled catheter (Vygon 71100.20 with an internal diameter of 1 mm) inserted through the tube lumen until 1 cm from the distal end, and a second catheter located at the proximal end of the tube. The catheters were connected with a luer-lock to our custom-made battery-powered device containing two pressure transducers (Fig. 1). The device collected the pressure waveforms and determined tube location. Synchronously, the waveforms were sent to a

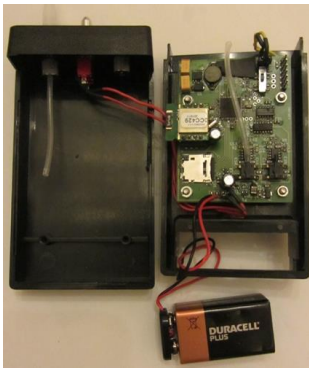

Figure 1: hand-held stand-alone diagnostic device

laptop through a Bluetooth connection for subsequent real time and off-line data analysis.

After a patient was considered eligible for inclusion, hemodynamic stability and adequate oxygenation confirmed by pulse oximetry were assured before the measurement was performed. Mechanical ventilation was stopped and the connecting piece was attached to the ETT and a self-inflating ventilation bag (Intersurgical, Wokingham, UK). The patient was ventilated 3 times by a nurse experienced in resuscitation, and asked to ventilate at her discretion as if it were the first ventilations after endotracheal intubation. The pressure waveforms and metadata were collected on a laptop. Subsequently, the connecting piece was detached and the mechanical ventilator was reconnected and mechanical ventilation resumed. The fully automatic algorithm was used in the data analysis. This algorithm first performs an automatic ventilation detection, and secondly performs the compliance and elastance calculations on each identified ventilation cycle. The calculated E-values and ∑-value are shown in figure 2. As a reference, the values of the tracheal and oesophageal ventilation pressure curves in healthy patients from our previous study[14], calculated with the same algorithms, are also presented. The specificity (ability to detect true tracheal intubation) of the algorithm was determined, when used in patients with pulmonary disease.

To determine the sensitivity and specificity more precisely, at a threshold D-value of 0.1, a Log(D-value) was calculated to obtain a parametric distribution of the D-values in each group. The mean and standard deviation (SD) of the distribution of log(D) was calculated for the three groups. From these mean (SD) values the normal distribution curve, and the sensitivity/specificity to detect oesophageal intubation was calculated assuming a threshold value of 0.1.

II4.4. Results

Mean (SD) age of the patients was 61 (15) years. Mean (SD) weight and height were 80 (18) kg and 173 (8) cm respectively, and 63% of patients were male. The mean (SD) body mass index was 27 (6) kg m^{-2}. The mean (SD) Murray score was 1.4 (0.6). The handheld device operated as expected, and generated D-values, in all patients in which it was

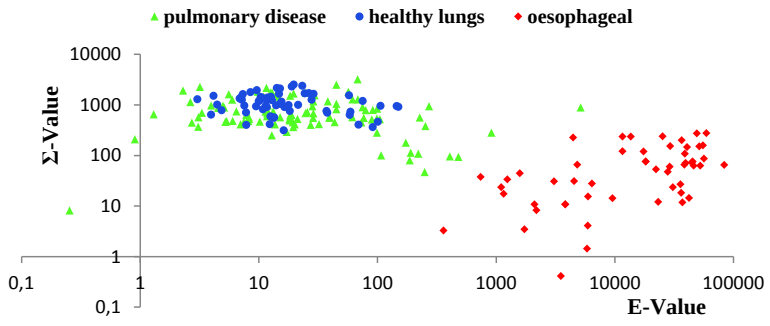

Figure 2: Scatterplot of Σ-values versus E-values of the first three tracheal ventilations in all patients with pulmonary disease (n=35), compared with the first three oesophageal (n=20) and tracheal (n=20) ventilations in elective patients without pulmonary morbidity. The dimension of the E-value is mmHg/sec ; the dimension of the Σ-value is mmHg x sec / 250

used.

A total of 105 ventilations in 35 patients were analysed. Lung pathologies present in the included patients included pneumonia, atelectasis and traumatic lung injury. Figure 2 shows the relationship between the E-values and ∑-values of the first three ventilations in each patient (n=35) with pulmonary disease in this study, compared with the first three oesophageal and tracheal ventilations in elective patients (n=2x20) in our former study[14] using the same automatic algorithm.

The median (IQR, range) peak ventilation pressure during the test ventilations was 18 (13-25, 8-36) cm H_2O. All D-values are presented in figure 3. The median (IQR, range) D-value was 34 (14-99, 0.17-832). All these values – as well as all of the D-values in the elective patients without pulmonary disease - were above the threshold value of 0.1, while 100% of oesophageal D-values were below this threshold value. When a grey zone of the D-value between 0.05 and 0.5 is applied, 6.7% (7 ventilations in 5 patients) of tracheal ventilations in lung diseased patients, and 3.4% (2 ventilations in 2 patients) of oesophageal ventilations would fall inside the grey zone. This results in a "very-high certainty" specificity of 95.8% and "very-high certainty" sensitivity of 96.6%, with a "moderately-high certainty" in 4.2% and 3.4% of tracheal and oesophageal intubations respectively.

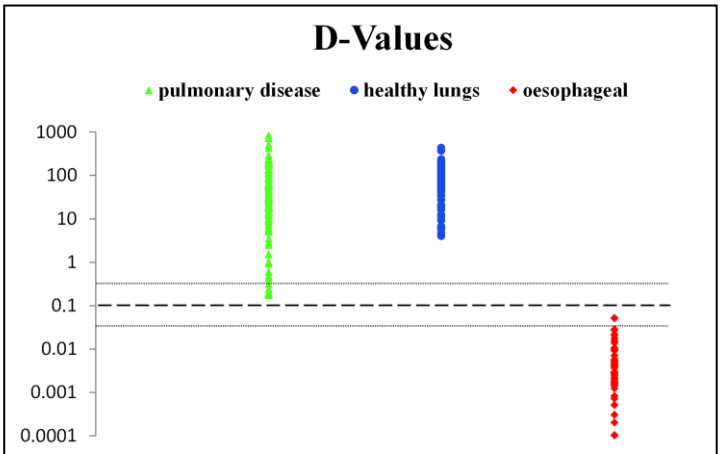

Figure 3: D-values of the first three tracheal ventilations in all patients with pulmonary disease (n=35), compared with the first three oesophageal and tracheal ventilations in elective patients without pulmonary morbidity. The dotted line shows a threshold value of 0.1. The fine lines show threshold values of 0.05 and 0.5.

The log(D-value) showed a parametric distribution with a mean (SD) D-value of 1.48 (0.89), 1.79 (0.48) and -2.63 (0.71) in the "lung disease tracheal", "elective tracheal", and "oesophageal ventilation" groups respectively, from which the corresponding probability distribution curves are shown in figure 4. Still considering a threshold value of 0.1, in patients with pulmonary disease and in patients with healthy lungs that would yield a specificity of 99.74% and 99.99% respectively, and a sensitivity of 98.94% to detect oesophageal intubation. The sensitivity/specificity at different threshold values are depicted in Table 1.

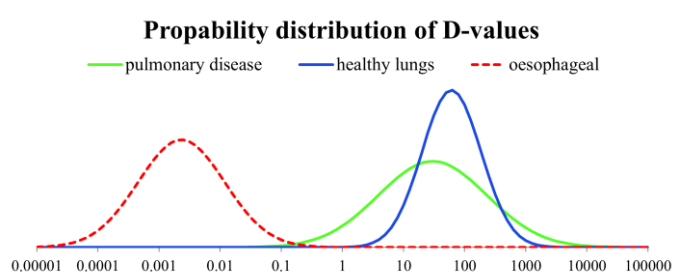

Figure 4: Probability distribution of D-values of tracheal ventilations in patients with pulmonary disease and of oesophageal and tracheal ventilations in elective patients without pulmonary disease.

Assuming the grey zone approach with threshold values of 0.1 and 1, the sensitivity/specificity analysis based on these probability distributions results in a "very-high certainty" specificity of 95.24% and 99.99% in diseased and healthy lungs respectively, and a "very-high certainty" sensitivity of 98.94%, with a "moderately-high certainty" sensitivity to detect oesophageal intubation of 99.99%.

D-value	pulmonary disease	healthy lungs	oesophageal
0.01	99.99	99.99	81.41
0.05	99.91	99.99	97.00
0.10	99.74	99.99	98.94
0.50	97.76	99.99	99.95
1.00	95.24	99.99	99.99

Table 1: sensitivity (tracheal) / specificity (oesophageal) to diagnose correct tube location as a function of the predetermined threshold D-values.

II4.5. Discussion

We have shown that the tracheal waveform analysis of synchronous pressure measurements can reliably confirm tracheal ventilation with near 100% specificity in patients with decreased pulmonary compliance. The integrated result of the analysis can be reported as a single value reflecting differences of flow and elastance of both systems. This permits a straightforward verification by medical practitioners of correct intubation. Using our device, one test ventilation immediately after intubation provides an instant diagnosis of tube (mis)placement within 2.5 seconds with a sensitivity and specificity of nearly 100%, even in patients with pulmonary disease.

In order to achieve this high sensitivity, an analysis of the dynamic pressure patterns during insufflation, as well as during expiration is necessary. Figure 2 shows that relying on only one variable is not sufficiently accurate. As previously explained[14] and depicted in figure 5, during insufflation an E-value is calculated reflecting the elastance (pressure increase for a given volume increase). It can be thought of as the gradient of the tangent of the tracheal pressure curve at the moment of the highest pressure increase. Technically, the E-value is calculated as $E = \frac{dP_{dist}/dt}{\Delta P/\Delta x} X P_{dist}$ at the moment of maximal increase in distal pressure (Fig. 5, γ) within a 300ms timeframe, with dP_{dist}/dt being the rate of distal pressure increase; $\Delta P/\Delta x$ being the pressure difference between the distal and the proximal measurement in the ETT (and as such

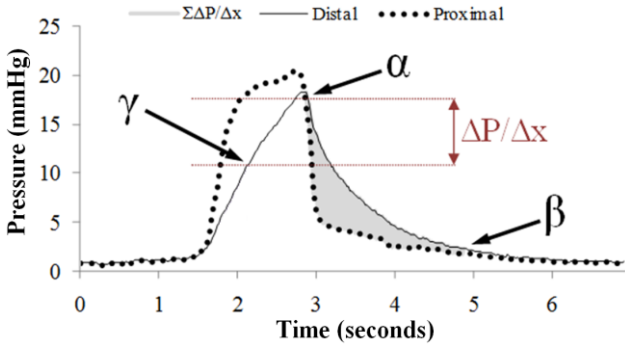

Figure 5: Example of tracheal distal and proximal pressure waveforms. The E-value is calculated at the moment of maximal increase in distal pressure, and reflects the elastance at point γ. The Σ-value is the area between the distal and proximal pressure curve (α-β) during exhalation (grey area) and reflects a volume of exhaled air.

a measure of inspiratory flow); and P_{dist} being the distal pressure. The ∑-value can be conceived as the volume of air exhaled during expiration, visualised as the grey area in figure 5. Mathematically it is defined as $\sum = \int_{\alpha}^{\beta}[P_{dist}\ x\ dt] - \int_{\alpha}^{\beta}[P_{prox}\ x\ dt\ ]$ expressed as mmHg x s, but since technically the pressure values are discrete measurements at 250 Hz, it is calculated as $\sum = \sum_{\alpha}^{\beta}[P_{dist} - P_{prox}]$, which is significantly less demanding for the CPU of the device. Consequently, ∑ is expressed as mmHg x sec / 250; E is expressed as $\frac{\text{mmHg/s}}{\text{mmHg}}\ x\ mmHg$, or mmHg/s.

In order to make the algorithm more predictable and computable, some substitutions of physiological variables by pressure values are performed: in determining elastance during inspiration, the flow is substituted by a pressure difference. Whereas the law of Hagen-Poiseuille describes the exact relationship between the pressure and flow, calculating the exact flow would unnecessarily complicate the computations, increasing the demand of the CPU, without improving the accuracy of the diagnosis, in particular since the variables in the Hagen-Poiseuille equation are either constant within one device (such as the diameter of the tube or the distance between measuring points), or not accurately known (such as the dynamic viscosity of the humid air, or the additional flow resistance due to the pressure catheter).

As such, from a physiological point of view, the E-value reflects the elastance of the lungs/oesophagus during insufflation, and therefore would in principle have as dimension mmHg/l; the ∑-value reflects the volume of exhaled air, in principle having a dimension l. The D-value, being $\frac{\sum}{\text{E}}$ would therefore have a dimension $\frac{\text{l}^2}{\text{mmHg}}$. For practical reasons however, no dimensions are used in the interpretation of the E-value, ∑-value or D-value.

Figure 2 shows that for neither the E-value nor the ∑-value on their own, a threshold value can be determined with an acceptably high sensitivity and specificity. Figure 3 however demonstrates that the ratio of both values, labelled the D-value, gives a 100% sensitivity and specificity in all our patient recordings when a threshold value of 0.1 is respected, both in patients with normal lungs and in patients with decreased pulmonary compliance. Because of the moderate number of patients included in our studies however, we cannot exclude that in exceptional cases a false diagnosis may be made. Therefore, in a fully-automatic system, we may envisage that a green or red LED-light is activated in case of a D-value above 0.5 or below 0.05 respectively. Indicators of "moderate certainty" may be used for D-values between 0.1 and 0.5 ("probably tracheal intubation"), and for D-values between 0.05 and 0.1 ("probably oesophageal intubation") respectively.

Because of the sensitivity and specificity being very close to 100%, the precise sensitivity and specificity calculated by conventional sensitivity analysis was undetermined. Therefore, a statistical approach was taken where the Log(D-value) was calculated to obtain a parametric distribution of the D-values in each group. Table 1 shows that in patients with healthy lungs, threshold values between 0.01 and 1 yield a very high specificity to exclude oesophageal intubation, while a threshold D-value of 0.5 and 1 yield a sensitivity to detect oesophageal

intubation of 99.95 and 99.99 respectively. In patients with diseased lungs, these threshold values result in a specificity 97.76 and 95.24 respectively. A sensitivity to detect oesophageal intubation of 99.99% is only reached with a threshold D-value of 1. This threshold value would result in a specificity of 95.24% in diseased lungs and 99.99% in healthy lungs respectively.

Because of the paramount importance of detecting oesophageal intubation, a threshold D-value of 1 should be advocated, even though a moderately lower specificity in patients with pulmonary conditions will result.

In a practical portable device, two "certainty" levels would be appropriate, reflecting a "very-high certainty" and "moderately-high certainty" diagnosis of correct ETT location. Therefore, a grey zone between 0.1 and 1 should be proposed, where a moderately-high certainty diagnosis would be concluded. D-values outside this grey zone correspond with a specificity and sensitivity of 99.99%

This study has several limitations. First of all, only tracheal ventilation measurements were performed in this patient population. For ethical reasons, oesophageal intubation and insufflation was deemed unacceptable in fragile intensive-care patients. Still, however, the aim of the study was to investigate the accuracy of the algorithm in patients with pulmonary conditions, and therefore only tracheal ventilations were deemed sufficient. Further, elastance and discriminative values are likely to be similar for oesophageal intubation regardless of the presence or absence of lung pathology. Still, it is unknown what the oesophageal pressure readings would be in ICU patients. Among other factors, raised intra-abdominal pressure may influence the pressure patterns during oesophageal ventilation. It is therefore important to acknowledge that the accuracies described reflect the sensitivity to detect tracheal ventilation in patients with pulmonary disease, while no firm conclusions can be drawn on the sensitivity to detect oesophageal intubation in ICU patients in general.

Secondly, the test ventilations to evaluate the diagnostic device were not performed in patients who were apnoeic or who had been resuscitated for several minutes. Nevertheless, the physiological conditions of the lungs in ventilated patients with normal tidal volumes which have not been recruited for at least ten minutes is the closest clinically feasible approximation of hypopnoeic patients in emergency situations. Since a recruitment manoeuvre in these patients is consistent with good clinical practice, it is appropriate to measure the pressure waveforms during such a recruitment manoeuvre.

Thirdly, only one type of ventilation device was used, and the manual ventilation manoeuvres may not have been identical to ventilations performed in a stressful emergency setting. The reported median (IQR) ventilation pressures of 18 (13-25) cm H_2O show rather conventional ventilation pressures. In addition, because the algorithm compensates for differences in ventilation pressure, this should not significantly alter the calculated D-value.

II4.5. Conclusion

Our previously published algorithm to detect oesophageal intubation retained its specificity in patients with decreased pulmonary compliance. We also demonstrated the feasibility to integrate sensors and diagnostic hardware in a small, portable hand-held device for convenient use in emergency situations. Further research will have to confirm our results in the out-of-hospital emergency setting.

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5

II5 Pressure measurement in cardiopulmonary resuscitation

II5.1 The cardiocirculatory system

The human body continuously needs oxygen and nutrient delivery towards the tissues in order to preserve homeostasis. Therefore the heart must preserve the blood flow, and the breathing muscles must preserve continuous air delivery to the longs. These two circulatory systems work in parallel by virtue of the heart muscle and the respiratory muscles. In the lungs, O_2 and CO_2 are exchanged between the air and the blood. Once either of those systems fails (due to primary failure of the muscle or because of obstruction somewhere in the circulatory system), oxygen delivery will become at risk. As soon as oxygen delivery stops, consciousness is lost within a few seconds, and irreversible brain damage occurs after a few minutes. Irreversible damage in other organs occurs after several minutes to hours.

II5.2 Principles of cardiopulmonary resuscitation

Cardiopulmonary arrest has many primary causes, but the immediate therapy consists of taking over the function of the failing systems : chest compressions and/or artificial ventilation. In both cases, pressure gradients are induced using external mechanical force to sustain the transport of blood/air. Compressing the chest induces direct compression of the heart between the chest bone and the spine, and simultaneously increases the pressure in the thoracic cavity. Both effects induce

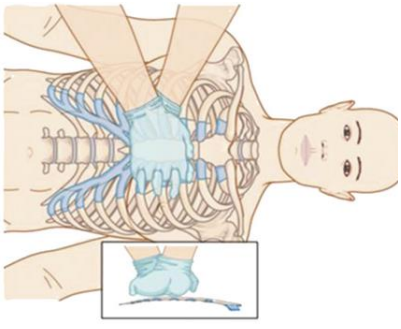

Figure 1: Compression positions for external chest compressions. A dominant hand is placed over the lower half of the sternum in the centre of the chest (Cha KC. J Emerg Med. 2013)

increased pressure in the heart and move blood towards the arterial system. Artificial ventilation (with a face mask or endotracheal intubation) creates an oscillating pressure gradient of air between the lungs and the external world with subsequent flow of air. In both cases, force is exerted (on the chest or on the ventilation balloon) which is supposed to result in a certain movement of blood/air. Exact measurements of the induced pressures have the potential to improve the quality of resuscitation and create an opportunity for improved automation.

II5.3 The cardiac versus thoracic pump

There are two postulated mechanisms of blood flow during cardiopulmonary resuscitation. The "cardiac pump" theory postulates that blood flows because the heart is squeezed between the chest bone and the spine. The "thoracic pump" theory postulates that blood flows from the thorax to the arterial system because of a general increase in intrathoracic pressure, compressing the heart from all directions. The intrathoracic pressure thus exceeds extrathoracic vascular pressure while the flow is restricted to the venous-to-arterial direction because of venous valves that prevent retrograde flow at the thoracic inlet.[1]

The‘cardiac pump’ mechanism consists of direct compression of the left and right ventricles between the sternum and vertebral column, creating a pressure gradient between the ventricle and the aorta (or pulmonary artery in the case ofthe right ventricle). The ventricle then refills during the decompression phase. For an optimal venous return, the intrathoracic pressure needs to be as low as possible

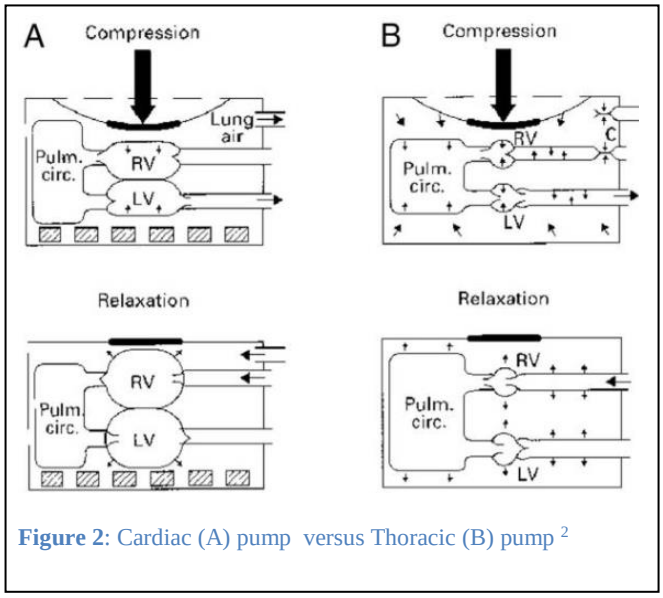

Figure 2: Cardiac (A) pump versus Thoracic (B) pump [2]

The “thoracic pump mechanism” is based on intrathoracic pressure swings due to chest compression, establishing an arteriovenous pressure gradient across the heart forcing blood to move down the gradient and to flow from the thoracic to the systemic circulation. For chest compressions to induce maximal intrathoracic pressure oscillations, a relatively high intrathoracic pressure must be sustained during the chest compression.

II5.4 Venous return

A first requisite to permit successful cardiac output, is that blood can fill the heart before compression/contraction starts. Blood circulation consists of blood being pumped out of the

heart, passing through the periferal tissues, and returning to the heart via the venous system. If the capacitance of the venous system is increased, or the total volume has decreased, this venous return can become inadequate, restricting the cardiac output and blood pressure. In addition, any condition that increases the intrathoracic pressure will decrease the venous return to the heart, thus ultimately negatively affecting the cardiac function.

II5.5 The thoracic pump & venous return : a difficult compromise

As a result of chest compression, the intrathoracic pressure waveform consists of a superposition of ventilation pressures and chest-compression induced oscillations (Fig. 3). Notice the much higher amplitude of the fast pressure oscillations at high ventilation pressures compared to low ventilation pressures.

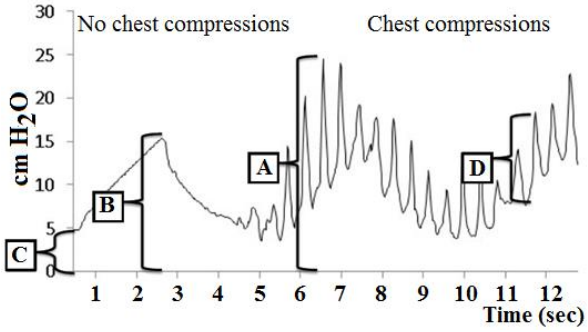

Figure 3: Illustration of peak airway pressure (A), peak ventilation pressure (B), positive end-expiratory pressure (C) and intrathoracic pressure variation ΔCP (D). Notice the variations in ΔCP during the ventilation cycle.

Optimising the ventilation pressures for maximal cardiac output during CPR requires balancing two counteracting factors:

1. An optimal venous return requires an intrathoracic pressure as low as possible - preferably negative (ie below atmospheric pressure).
2. An optimal thoracic pump function requires an intrathoracic pressure considerably higher than conventional pressures.

Moreover, the intrathoracic pressure for an optimal thoracic pump is different for every patient, and is dependent on chest anatomy. This indicates that individualised optimisation of the intrathoracic pressure is arguably necessary to optimise the hemodynamic effectiveness of the chest compressions.

II5.6 The Thoracic pump : Unravelling the effect of compression and ventilation.

Adapted from Resuscitation 2010; 81S: S1–S114: AS033
Kalmar A.F., De Smedt L.E.G., Maertens V.L., Absalom A., Monsieurs K.G.

The intrathoracic pressure variation (ITPV) during resuscitation results from pressure generated by chest compression and ventilation. Consequently, a certain intrathoracic air volume within the lungs is necessary to optimise the intrathoracic pressure variations and therefore also the "thoracic pump" induced by chest compressions. In order to quantify this interaction, we studied the relation between chest compression depth, ventilation pressure and ITPV during resuscitation.

After approval by the Ethics Committee of Ghent University Hospital, 51 patients undergoing out-of-hospital resuscitation by a physician-staffed team were included. The compression depth (CD) during manual chest compression was measured using an accelerometer (Zoll, US). After intubation, the airway pressure (a surrogate for intrathoracic pressure) was measured and recorded. In a subsequent offline data analysis, the accelerometer and airway pressure data were synchronised offline using custom Visual Basic code in Excel. For every chest compression, ITPV (the difference between the compression-induced peak and nadir pressure) was separated from the concomitant ventilation pressure (Pvent). The relationship between ITPV and CD was analysed with linear regression for a CD range of 2.5–6 cm. The ranges of ventilation pressure 0–10 and 10–30cm H_2O were analysed separately because of a breakpoint in the regression line. In order to weigh each patient equally, the median ITPV value at each Pvent or CD within each patient was used for regression analysis.

The relationship between ITPV and Pvent was described as follows: ITPV = a * Pvent + b

For Pvent 0–10cm H_2O : ITPV = 2*Pvent + 6 ($R^2 = 0.96$)

For Pvent 10–30cm H_2O : ITPV = 0.6*Pvent + 29 ($R^2 = 0.94$)

The relationship between ITPV and CD was as follows: ITPV = a * CD + b

For CD 2.5–6 cm : ITPV = 0.3*CD + 19 ($R^2 = 0.82$)

This shows that an increase of Pvent from 0 to 10 cm H_2O increased ITPV with 20cm H2O, while an increase of CD by 2 cm increased ITPV by only 0.6cm H_2O.

These findings suggest that the effect of chest compression depth on ITPV is small, but can be increased very significantly by Pvent. Further studies are needed to investigate the relation between ITPV, cardiac output and survival.

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6

II6 Methods and systems for ventilating or compressing

US 20130085425A1

United States
Patent Application Publication

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Pub. Date: Apr. 4, 2013

Adapted from : "methods and systems for ventilating or compressing"
Date of PCT filing : Jun. 09. 2011
Inventors : K Monsieurs, **AF Kalmar**

Abstract

A system for providing control signals for ventilating or compressing, respectively, includes an information receiving device that receives, for a resuscitation, information regarding a compression parameter and/or ventilation parameter, as function of a parameter indicative of blood circulation, a processing component for evaluating the different values of the chest compression parameter and/or ventilation parameter as function of the parameter indicative of blood circulation and deriving based on said information a value for the ventilation parameter and/or chest compression parameter respectively, and a control signal generator for generating control signals according to the derived ventilation parameter or chest compression parameter.

II6.1 Field of the invention

The present invention relates to a medical device for analysing resuscitation, for example in case of intubation of a patient, or for optimising chest compression depth and ventilation pressure.

II6.2 Background of the invention

When a patient needs positive pressure ventilation or chest compression (resuscitation), a number of clinical problems may arise :

1. ***The Lazarus phenomenon***
   There are numerous case reports of restoration of a spontaneous circulation after cessation of resuscitation efforts. This phenomenon, also referred to as the "Lazarus phenomenon" is mainly explained by trapping of air during ventilation and the presence of "positive end expiratory pressure" (PEEP) resulting in inefficacy or failure of the resuscitation. As trapped air escapes and the positive end expiratory pressure disappears after cessation of the resuscitation, this may allow blood to start flowing to the heart again and therefore result in restoration of circulation even after CPR efforts have been stopped.
2. ***Hyperventilation***
   Animal studies have also shown that hyperventilation during resuscitation results in decreased coronary perfusion pressure and in excess mortality. In a small clinical observational study of 13 patients with cardiac arrest, high ventilation rates and increased intrathoracic pressures were recorded. Early detection and avoidance of hyperventilation and subsequent increased intrathoracic pressures during resuscitation may be an accurate means for preventing failure of resuscitation and for increasing survival chances and therefore is an important clinical issue.

Current state of the art methods to assess quality of resuscitation mainly use impedance measurement of the chest wall and accelerometers placed on the breastbone. The quality of ventilation is often currently addressed by impedance measurements between two electrodes attached to the chest of the victim. This provides reasonably accurate measurements of ventilation frequency and very rough measurements of volume. The quality of chest compression is determined by accelerometers placed on the breastbone of the victim. These provide reasonably accurate measurements of compression frequency and dept.

All these technical solutions to improve the quality and safety of intubation, ventilation and chest compression are in their early stages of clinical application and there is room for improvement.

II6.3 Summary of the invention

Advantages of the present invention :

1. to provide good methods and systems for controlling ventilation and/or compression adapted to the requirements of the individual patient.

2. an individualized resuscitation method can be obtained, optimized for the patient treated at that moment. This allows determining the cardiac and thoracic pump potential during resuscitation in individual patients, thus also allowing individual, patient-dependent, optimization of the cardiac output.

3. Anatomical and physiological differences between patients can be taken into account as values of individual measurements are used for optimizing the ventilation and compression specifically for the individual patient.

4. A more efficient resuscitation can be provided. The information may comprise information regarding a chest compression parameter and/or ventilation parameter as function of a tracheal pressure difference by chest compression. The latter may be a parameter indicative of blood circulation. Pressure differences occurring upon chest compression or blood circulation show an optimum for a given ventilation volume. Determination of the optimal ventilation conditions for obtaining optimum pressure difference occurring upon chest compression – and therefore an optimum thoracic pump - can thus be performed, which may result in optimum blood circulation.

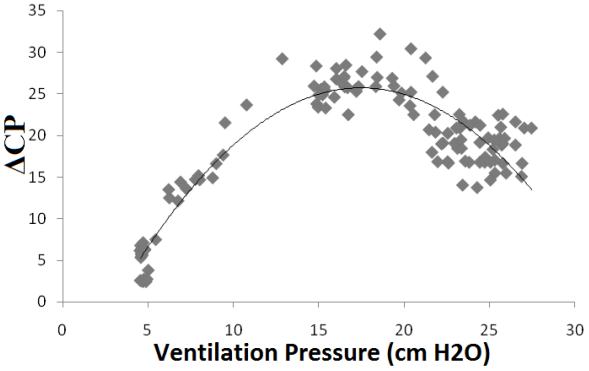

Figure 1: The effect of ventilation pressure on the amplitude of the intrathoracic pressure oscillations (ΔCP).

5. An automated ventilator or compressor can be obtained whereby the optimum is found through a feedback loop, resulting in patient optimized conditions without the risk for applying too strong ventilation or compression. An iterative algorithm may be conceived to optimise ventilation pressure and compression depth for optimal intrathoracic pressure variation (ΔCP) with minimal impact on venous return.

II6.4 Example of an application

We performed a study in 45 patients where an out-of-hospital cardiopulmonary resuscitation was performed and airway pressure was measured at the proximal end of the endotracheal tube. The pressure difference by chest compression ΔCP was determined for each chest compression and the ventilation pressure VP at the time of compression was calculated. The pressure difference by chest compression ΔCP is a parameter indicative of the blood circulation. A high pressure difference may allow for a good blood circulation. Statistical analysis was performed to explore the relationship between pressure difference by chest compression ΔCP and ventilation pressure VP. Figure 2 indicates the variability in pressure difference by chest compression ΔCP within and between individuals. Individual patients are sorted by increasing median for the pressured difference by chest compression ΔCP. For each patient, the median, 25th and 75th percentile (box) and the 10th and 90th percentile (whiskers) of the recorded ΔCP's are shown. The pressure difference by chest compression ΔCP ranged from 0 cm H_2O to 82 cm H_2O. The median value for pressure difference by chest compression ΔCP was 31 cm H_2O. Initially a positive correlation between pressure difference by chest compression and ventilation pressure was found. When ventilation pressure initially increased from 0 to 15 cm H_2O, the pressure difference at chest compression ΔCP was almost 4 times amplified. The latter can be seen in figure 3 correlating the initial pressure difference by chest compression and ventilation pressure.

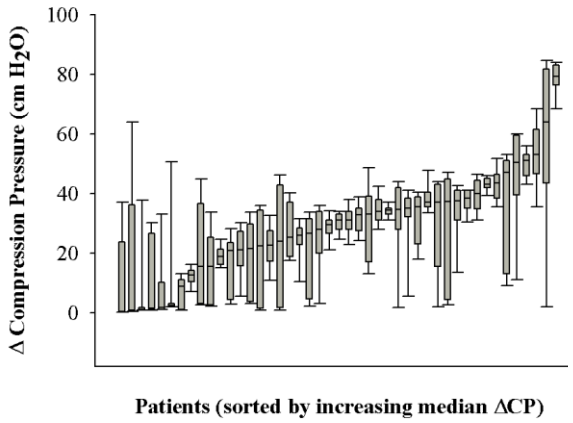

Figure 2: Variability in ΔCP within and between individuals

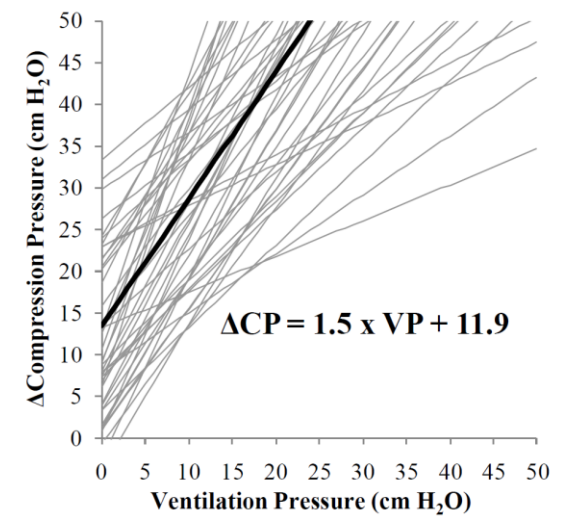

Figure 3: Correlation between ΔCP and VP

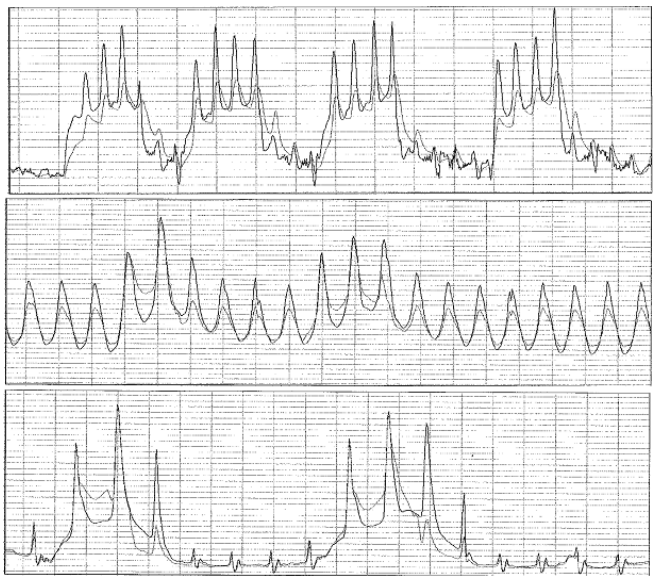

Figure 4: Effect of ventilation pressure on ΔCP in three different patients

Forward blood flow during cardiopulmonary resuscitation (CPR) is believed to be the result of direct compression of the heart (the "cardiac pump") and intrathoracic pressure (ITP) differences (the "thoracic pump"). The ITP during CPR is a combination of pressure generated by ventilation (VP) and pressure differences generated by chest compression (ΔCP). Not only can chest compression be optimized by selecting a ventilation pressure, but also for different patients, different resuscitation conditions should be applied, since the pressure difference generated by chest compression varies greatly within and between patients. The obtained pressure profile for the individual patient may depend on the age, gender, stiffness of the thoracic wall, etc. Consequently, also the optimum conditions for resuscitation of individual patients differ significantly, as can be taken into account using embodiments of the present invention.

7

II7 Excessive chest compression rate is associated with insufficient compression depth in prehospital cardiac arrest.

Resuscitation. 2012 Nov;83(11):1319-23.

Monsieurs KG, De Regge M, Vansteelandt K, De Smet J, Annaert E, Lemoyne S, Kalmar AF, Calle PA.

II7.1 Abstract

Background and goal of study: The relationship between chest compression rate and compression depth is unknown. In order to characterise this relationship, we performed an observational study in prehospital cardiac arrest patients. We hypothesised that faster compressions are associated with decreased depth.

Materials and methods: In patients undergoing prehospital cardiopulmonary resuscitation by health care professionals, chest compression rate and depth were recorded using an accelerometer (E-series monitor/defibrillator, Zoll, USA). Compression depth was compared for rates <80/min, 80–120/min and >120/min. A difference in compression depth ≥0.5 cm was considered clinically significant. Mixed models with repeated measurements of chest compression depth and rate (level 1) nested within patients (level 2) were used with compression rate as a continuous and as a categorical predictor of depth. Results are reported as means and standard error (SE).

Results and discussion: One hundred and thirty-three consecutive patients were analysed (213,409 compressions). Of all compressions 2% were <80/min, 62% between 80 and

120/min and 36% >120/min, 36% were <4 cm deep, 45% between 4 and 5 cm, 19% >5 cm. In 77 out of 133 (58%) patients a statistically significant lower depth was observed for rates >120/min compared to rates 80–120/min, in 40 out of 133 (30%) this difference was also clinically significant. The mixed models predicted that the deepest compression (4.5 cm) occurred at a rate of 86/min, with progressively lower compression depths at higher rates. Rates >145/min would result in a depth <4 cm. Predicted compression depth for rates 80–120/min was on average 4.5 cm (SE 0.06) compared to 4.1 cm (SE 0.06) for compressions >120/min (mean difference 0.4 cm, $P < 0.001$). Age and sex of the patient had no additional effect on depth.

Conclusions: This study showed an association between higher compression rates and lower compression depths. Avoiding excessive compression rates may lead to more compressions of sufficient depth.

II7.2 Introduction

Following the International Consensus on Science and Treatment Recommendations on Resuscitation, the European Resuscitation Council (ERC) 2010 Guidelines for Cardiopulmonary Resuscitation (CPR) recommend for rescuers to compress the sternum of an adult victim of cardiac arrest "at least 5 cm (but not more than 6 cm)" at a rate of "at least 100/min (but not more than 120/min)".[1,2] The previous ERC Guidelines (2005) recommended to compress the sternum "4 to 5 cm" at a rate of "about 100/min".[3] The main reason for this change in guidelines are studies showing that deeper compression depth is associated with higher success of defibrillation and a higher chance of admission to hospital.[4,5] Therefore, sufficient compression depth is key to survival. Professional rescuers, however, often do not deliver high quality CPR regarding compression rate and depth.[6–8] The reasons for this are not fully known. Recently, Field et al. found that compression depth decreased from 4.0 cm at 80/min to 3.5 cm at 160/min when health care professionals performed continuous compressions on a manikin.[9] Their results suggest an inverse relationship between compression rate and depth. The latest Consensus on Science and Treatment Recommendations on Cardiopulmonary Resuscitation (2010) recognised the knowledge gaps in the relationship between compression rate and depth.[1] In order to characterise the relationship between compression rate and depth, we performed an observational study in prehospital cardiac arrest patients.

II7.3 Methods

II7.3.1 Aim of the study

The aim of the study was to quantify the relationship between compression rate and compression depth during prehospital cardiac arrest by professional rescuers. Our hypothesis was that higher compression rate is associated with lower compression depth.

II7.3.2 Procedure

This observational study was conducted in the Ghent area with a population of approximately 150,000 inhabitants. From March 2009 until October 2010 all prehospital resuscitation events attended by the physician-staffed second tier ambulance of Ghent University Hospital were registered with a Zoll E-series defibrillator and CPR-D Padz® (Zoll, Chelmsford, USA) The ambulance was staffed by an emergency medical technician, a nurse specialised in emergency medicine and a resident or consultant in emergency medicine or anaesthesiology. ERC Guidelines 2005 were followed.

All patients were resuscitated on a solid surface. In most cases, a first tier ambulance staffed with two emergency medical technicians would also be at the scene, ensuring chest compression during advanced life support. The Ethics Committee of Ghent University Hospital approved the study and allowed deferred consent.

II7.3.3 Materials

Immediately after arrival of the second tier ambulance, CPR-D Padz® were placed on the victim's chest according to the manufacturer's instructions. The CPR-D Padz® incorporate an accelerometer measuring displacement of the chest during compressions. The defibrillator provided real-time audible and visual feedback of compression quality (rate and depth). A sliding window of five compressions was analysed. If the recorded depth failed to achieve 4 cm in three of the five compressions, the unit periodically generated a voice prompt saying, "push harder" When the four cm threshold was achieved in two of three compressions, the "good compression" voice prompt was played. According to the manufacturer, the accuracy of the compression depth measurement was ±0.6 cm 95% of the time.[10] Compression rates below 80/min resulted in the automatic activation of a metronome sounding at a rate of 100/min. In addition to the audible feedback, visual feedback was provided consisting of a display showing a vertical bar for every compression indicating depth, plus a horizontal bar indicating overall good compression depth and rate when full. As an inherent feature of the Zoll software, potentially excessive compression depth or rate was not corrected.

II7.3.4 Data collection

For every compression, the defibrillator automatically stored depth, rate and a time stamp on a memory card that was uploaded after the event with RescueNet™ Code Review, Enterprise Edition version 5.[12] (Zoll, Chelmsford, USA). The resulting files were exported in a text format and imported into Excel for Windows. For each compression the rate was then calculated using the time interval to its preceding compression. Therefore the first compression of a series of compressions was not taken into account. Data on sex of the patient, age, presenting rhythm and return of spontaneous circulation were extracted from the ambulance run sheets.

II7.3.5 Inclusion and exclusion criteria

Inclusion criteria for analysis were: presence of informed consent and age of 18 years or more. Exclusion criteria for analysis were the absence of a data file (accelerometer not applied or a technical problem), an incomplete data file or resuscitation performed in a driving ambulance generating random compression data.

II7.3.6 Statistical analysis

To examine the relationship between chest compression depth and rate, a mixed model was used with repeated measurements of chest compression depth and rate (level 1) nested within patients (level 2). Multilevel models have several advantages: they use all available data, can properly account for correlation between repeated measurements on the same subject, can handle missing data adequately, and have great flexibility to model time effects.[11–13] Different specifications of the variance-covariance structure were considered and model selection was based on the procedures described in Verbeke and Molenberghs,[11] information criteria (Akaike Information Criterion, Bayes Information Criterion) and interpretability of the results. First, a mixed model was estimated with chest compression depth as criterion, fixed linear and quadratic effects for chest compression rate as time-varying predictors, age and sex as time-invariant covariates, and random intercepts and random linear (subject-specific) slopes as random effects. For inference on the fixed effects, the Kenward–Roger denominator degrees of freedom method was used. This model (without the terms that were not significant) was used to make compression depth estimates (and 95% confidence intervals) at particular values of compression rate. In addition, a similar mixed model was estimated but with compression rates divided into a categorical variable comprised of three categories: <80/min, 80–120/min, and >120/min. P-Values are reported as two-tailed.

$P \leq 0.05$ was considered significant. Statistical analysis was performed using Statistical Analysis Software (SAS) (version 9.2, Cary, NC, USA).

II7.4 Results

II7.4.1 Demographics

Demographic data are shown in Table 1.

	Included patients N=133 (83%)	Excluded patients N=28 (17%)	P-Values
Age (years)	67 (16)	61 (18)	0.13
Female	41 (31%)	6 (21%)	0.32
Initial Rhythm			0.32
Asystole	93 (70%)	17 (61%)	
VF/VT	18 (14%)	4 (14%)	
PEA	22 (16%)	7 (25%)	
ROSC	56 (42%)	15 (53%)	0.27

Table 1: Demographics. SD: standard deviation; VF: ventricular fibrillation; VT: ventricular tachycardia; PEA: pulseless electrical activity; ROSC: return of spontaneous circulation. Values as mean (SD) or count (percentage).

II7.4.2 Compression data

Out of the 161 eligible patients, 133 patients could be analysed. Each subject had on average 1605 (SD 1068, min 86, max 5108) repeated measurements of chest compression rate and depth (a total of 213,409 compressions).

Fixed effects	Regression weight (SE)	F test (df, df)	P-Values
Linear effect rate (/ min)	0.03287 (0.002084)	F(1, 163) = 248.77	<0.0001
Quadratic effect rate (/ min)	−0.00019 (0.000003)	F(1, 210,000) = 3840.31	<0.0001
sex	0.03140 (0.1417)	F(1, 130) = 0.05	0.83
Age	−0.00772 (0.004136)	F(1, 130) = 3.49	0.06

Table 2: Demographics. SD: standard deviation; VF: ventricular fibrillation; VT: ventricular tachycardia; PEA: pulseless electrical activity; ROSC: return of spontaneous circulation. Values as mean (SD) or count (percentage).

Of all compressions, 36% were <4 cm deep, 45% between 4 and 5 cm, 19% >5 cm, 2% were <80/min, 62% between 80 and 120/min and 36% >120/min. Thirty percent of all compressions were performed with a correct depth and rate according to the ERC 2005 Guidelines. Figure 1 shows the distribution of compression depth per rate category. In 95 out of 133 (71%) patients the mean compression depth in the rate category >120/min was lower than in the category with compression rate between 80 and 120/min; in 77 out of 133 (58%) this difference in compression depth was statistically significant. In 40 of 133 (30%) the difference was considered clinically significant because the mean depth decreased with 0.5 cm or more. Table 2 shows the results of the mixed model that examines the relation between chest compression rate and depth with age and sex of the patient as covariates.

The linear regression weight for compression rate (0.03) indicates that chest compression depth increases with increasing chest compression rate but the negative quadratic regression weight for chest compression rate2 (−0.0002) indicates that this linear increase levels off and turns into a decrease in chest compression depth at higher chest compression rates. This is illustrated in figure 2, showing that chest compression depth slowly increases for chest compression rates between 20 and 86/min; from then on, a higher chest compression rate results in a smaller chest compression depth (first slowly but later on more quickly).

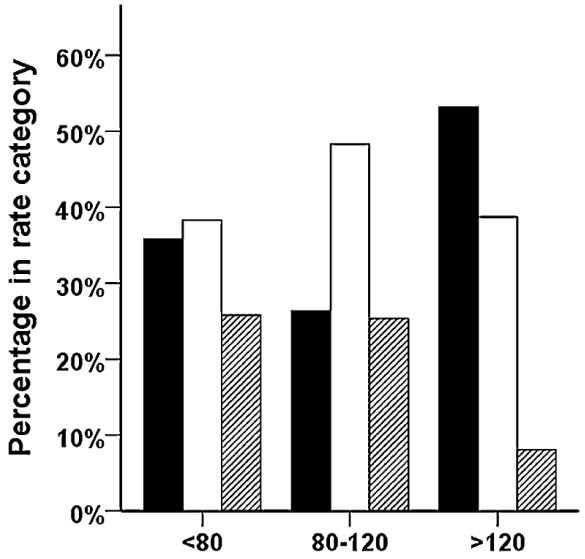

Figure 1: Distribution of depth according to rate category. Black bars indicate <4 cm depth, white bars 4–5 cm depth, crossed bars >5 cm depth.

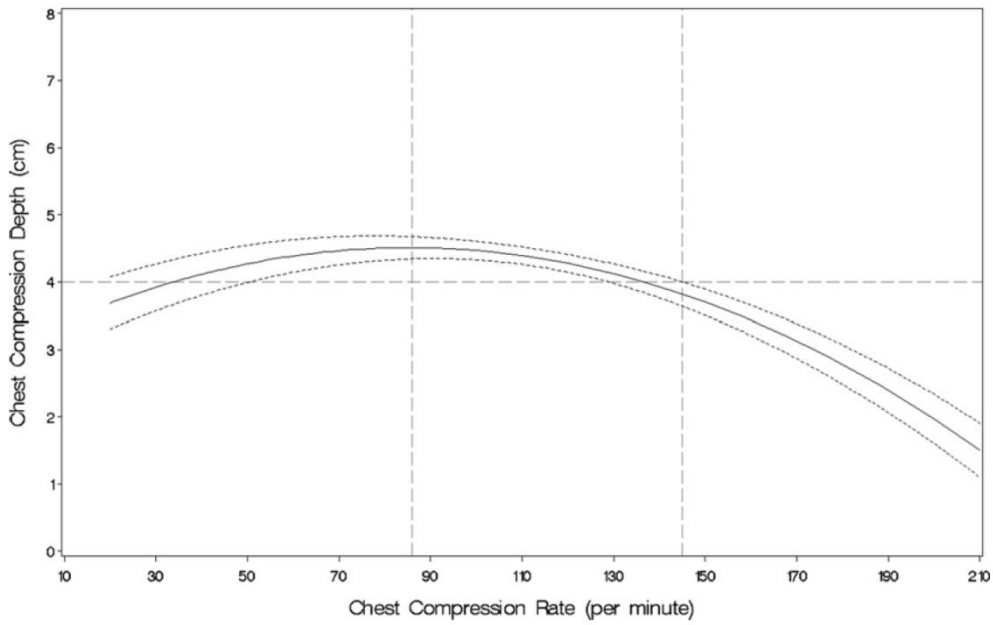

Figure 2: Relationship between chest compression rate and depth. Horizontal line indicates minimum compression depth (4 cm) according to ERC 2005 Guidelines. Vertical lines indicate compression rate with deepest compression depth (86/min), and compression rate when higher rates generate insufficient compression depth (145/min). Interrupted lines indicate 95% confidence intervals.

At 86/min, the deepest chest compression is predicted being 4.5 cm (95% CI 4.3–4.7). At 100/min and 120/min, the estimated chest compression depths are 4.5 cm (95% CI 4.3–4.6) and 4.3 cm (95% CI 4.1–4.4), respectively. Rates of more than 145/min would result in depths below 4 cm (the upper 95% CI limit of the estimated depth at a rate of 145/min is 4 cm implying that under resampling the estimated compression depth at 145/min would be below

4 cm in 95% of the cases). At lower compression rates, compression depth remains fairly stable and only at a predicted rate of 34/min, compression depth reaches the lower limit of 4.0 cm. Very low compression rates were uncommon, therefore the clinical significance of this finding is limited.

In general, we conclude that compression depth remains above 4 cm over a wide range of rates, but excessively fast compressions lead to insufficient depth. Furthermore, Table 2 shows that there are no significant effects of age and sex of the patient. Next, a mixed model was used with chest compression rate as a categorical predictor. Categorisation according to the 2005 Resuscitation Guidelines resulted in very unbalanced categories: 2% (<80/min), 62% (80–120/min) and 36% (>120/min).

The estimated chest compression depth for the three categories is depicted in Table 3. This analysis confirms that chest compression depth is significantly different between the three categories, $F(2, 210{,}000) = 4424.94$, $P < 0.0001$. In line with figure 2, chest compression depth was maximal at a chest compression rate in the category 80–120/min and less deep in the adjacent categories. This model also shows that age and sex were not significantly different, respectively, $F(1, 130) = 1.56$, $P = 0.21$, $F(1, 130) = 0.05$, and $P = 0.82$.

	Least square mean estimate (SE)
<80/min	4.35 (0.06)
80–120/min	4.45 (0.06)
>120/min	4.08 (0.06)

Table 3: Prediction of chest compression depth (cm) based on chest compression rate divided into three categories with age and sex as covariates: estimated means. SE: standard error. All three means differ pairwise at P < 0.0001 in an adjusted Tukey–Kramer comparison.

II7.5 Discussion

We showed that, during prehospital resuscitation by professional rescuers, compression rates between 80 and 120/min were associated with deeper compression depths as compared to rates >120/min. A difference of 0.5 cm depth was considered clinically significant because Edelson and colleagues showed that every 0.5 cm increase in compression depth doubled the odds of successful defibrillation.[4] Moreover, using a multilevel model we showed that the predicted deepest compression depth (4.5 cm) occurred at a rate of 86/min. From thereon, compression depth declined gradually and only at a rate of about 145/min compression depth would become unacceptably low according to the ERC Guidelines 2005.

Our findings support the results from a manikin study by Field et al. showing that faster compressions lead to reduced compression depth.[9] In our study, high compression rates were common and may be explained by stress or by the inability of rescuers to assess and control the compression rate. Very low compression rates were uncommon and may be associated

with specific activities potentially interrupting chest compressions such as aspiration, intubation and defibrillation.

We have measured compression depth and rate using accelerometer technology with feedback. Feedback during CPR has shown to improve the quality of CPR but an effect on survival has not been demonstrated.[14,15] The Zoll defibrillator did not correct rescuers who compressed too fast. On the other hand, the defibrillator activated a metronome at 100/min when compression rate was <80/min. Manikin studies have shown that a metronome not only guides compression rate but can also increase or decrease compression depth.[9,16–19] Chung and colleagues reported that an increase in rate also increased compression depth in a manikin study. [17] This is in contrast with the findings by Field et al. who reported the opposite.[9] Potential explanations for the decrease in compression depth in the Field study may be the longer compression periods as compared to the Chung study (2 min versus 1 min), the shorter recovery periods between each compression period (3 min versus 20 min), and the higher compression rates (up to 160/min versus 140/min), all potentially leading to more fatigue and probably reflecting reality better.

To prevent loss of compression depth, rescuers should be advised not to compress at rates exceeding 145/min. The mechanism whereby excessively fast compressions lead to insufficient depth is unknown, but may be linked to patient-related factors such as chest mechanics, and rescuer-related factors such as physical inability to deliver deep compressions at high rates and fatigue.

A first limitation of the study is that the results were obtained with specific feedback provided by the Zoll E series defibrillator. Because the specific instructions by the defibrillator were not recorded, it is unknown to what extent rescuers followed the instructions and how they were influenced by them. Furthermore, it cannot be excluded that other feedback systems may influence the relationship between compression depth and rate differently. Second, apart from age and sex, other patient factors such as chest compliance are likely to influence the relationship between compression rate and depth, but because the Zoll technology does not incorporate a pressure sensor, we were unable to measure them.[20] Third, rescuer-related characteristics (weight, height, fatigue) were not studied because during a resuscitation attempt by an advanced life support team several rescuers alternate at delivering compressions and it is currently not possible to determine the individual contribution of each rescuer. Fourth, although incomplete release is an important determinant of the quality of resuscitation, the defibrillator was not able to measure it. Fifth, our study was performed using feedback according to ERC Guidelines 2005. As the ERC Guidelines 2010 recommend a depth of “at least 5 cm”, this may change to relationship between compression rate and depth.

II7.6 Conclusions

Using a defibrillator with an accelerometer measuring compression rate and depth, in about one third of cardiac arrest patients compression rates >120/min were associated with a clinically significant lower compression depth as compared to compressions of <120/min. In a predictive model, deepest compressions were provided at a rate of 86/min, and a depth of <4 cm occurred at a compression rate of >145/min. Avoiding excessive compression rates may lead to more compressions of sufficient depth.

II7.7 Conflict of interest statement

The authors report no conflict of interest related to the study.

II7.8 Acknowledgments

We are grateful to the nursing and medical staff of the Emergency Department for resuscitating the patients and to Charlotte Van Keirsbilck for providing administrative and logistic support to the project.

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III

Optimisation of intracranial pressure measurement during neuroendoscopy.

1

III1 Intracranial pressure during neuroendoscopy

III1.1 Anatomy of the ventricle system

The ventricular system is a set of four interconnected cavities (ventricles) in the brain. The ventricles are filled with cerebrospinal fluid (CSF) which bathes and cushions the brain and spinal cord within their bony confines. CSF flows from the lateral ventricles into the third ventricle, and then the fourth ventricle. From the fourth ventricle it can pass into the central canal of the spinal cord.

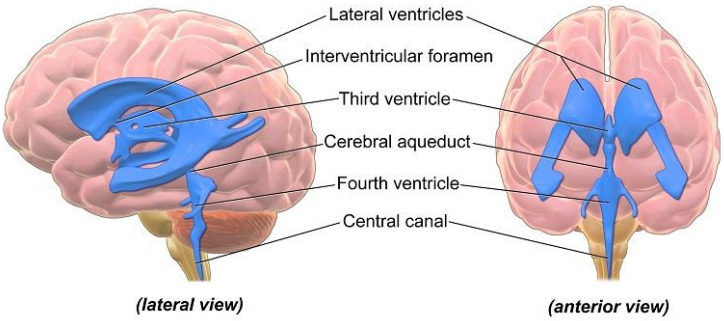

Figure 1: The ventricular system
Source: Wikimedia creative commons

III1.2 Cerebral Perfusion pressure

The cranium can be considered as a box with three components: blood, cerebrospinal fluid (CSF), and brain tissue. While both the blood and CSF have poor compression capacity, the brain is easily compressible. If the pressure inside the cranium increases, the blood vessels are compressed, which can ultimately result in a decreased blood supply of the brain. In normal conditions, the intracranial pressure is low, thus the cerebral perfusion pressure = mean arterial pressure – venous pressure (CPP = MAP – VP). If however the intracranial pressure (ICP) becomes higher than the venous pressure, then CPP = MAP – ICP.

III1.3 Neuroendoscopic procedures

Neuroendoscopy is a minimal-invasive technique, often used to cure hydrocephalus, take biopsies or removing tumors or cysts. During neurosurgical procedures, an endoscope is advanced through a burrhole in the skull, into the lateral ventricles, and further advanced into the third ventricle.

A neuroendoscope consists of a long tube with several channels inside. Typically, there is an inspection lumen for receiving a visualisation instrument (*e.g.* camera, fiber optic or rigid optic), two rinse lumina and one or two working channels to insert instruments. A rinse inlet lumen allows passage of fresh rinse medium (generally aqueous saline solution) to the distal tip of the endoscope, while a rinse outlet lumen provides a passage for removal of waste rinse medium from the intervention site.

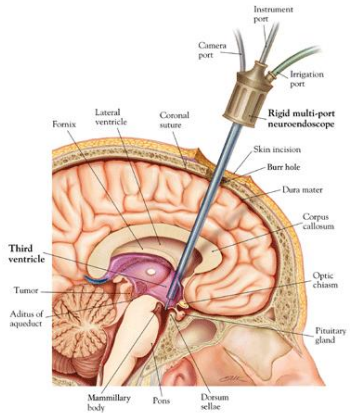

Figure 2: depiction of a neuro-endoscope in the ventricular cavities.

Li KW, NelsonC, Suk I, Jallo GI
Neuroendoscopy: past, present and future. Neurosurg Focus. 2008; 19: E1
With permission

III1.4 intracranial hypertension during neuroendoscopy

At high rinsing rates, very swift increases in ICP can occur, up to a level higher than the MAP. This implies a high risk of severe complications such as retinal ischemia (blindness), stroke, or hemodynamic adverse effects. While rinsing at high flow can increase the intracranial pressure dangerously, even in cases of low rinsing rates, debris floating in the rinsing fluid may obstruct the outflow channel, still inducing a high ICP. As a consequence, it is imperative during these procedures to have an accurate measurement of the ICP to guide the surgery and rinsing process.

III1.5 Clinical evidence of unreliable conventional ICP measurement

During routine neuro-endoscopic procedure, the conventional method to monitor the ICP is connecting a pressure transducer to the outflow channel of the neuro-endoscope. There were however several observations of Cushing reflexes – suggesting considerably increased ICP – which were not observable by this type of monitoring. This is illustrated[1] in chapter III.2, and was also one of the conclusions of our publication in the British Journal of Anesthesiology.[2]

III1.5 In-vitro evaluation of advanced ICP measurement

In order to quantify the (in)accuracy of conventional ICP-measurement, and to evaluate a superior alternative, a model of neuro-endoscopy was produced and measurements at several potential locations were performed. Ultimately, a new device was developed, and evaluated which meets all the requirements for practical use during neuro-endoscopic procedures.[3] Because of the market potential, Patent protection was applied for and granted in 2014.[4]

III1.6 Development of new applications of the device

Interestingly, the hardware developed for our neuroendoscopic applications could also be further developed as a fundamentally new approach for central-venous access, and other applications, which could offer significant medical advantages, and a considerable market potential. Therefore, this was further developed into a prototype to perform in-vitro and in-vivo tests. Again, patent protection was applied for and granted in 2014.[5]

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PCT/EP2009/066851
United States Patent and Trademark Office: Granted 2014
European Patent Application N° 2598015: Granted 2014

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Capillary tube assembly
PCT/EP2011/062810
United States Patent and Trademark Office: Granted 2014
European Patent Application: Granted

2

III2 Total brain ischemia during normal intracranial pressure readings due to obstruction of the outflow of the endoscope

Adapted from:

J Neurosurg Anesthesiol. 2005 Jul;17(3):175-6.
Kalmar AF, Van Aken J, Struys MM.

III2.1 Introduction

In neurosurgery, as in many surgical disciplines, the use of minimal invasive approaches using the endoscope is progressively increasing[1]. During these procedures, the ventricular cavities are rinsed continuously. This rinsing inside the fixed volume of the intracranial cavities may cause a sudden increase of the intracranial pressure (ICP). Since the cerebral perfusion pressure (CPP) equals the mean arterial pressure (MAP) minus the ICP, the CPP decreases linearly with the increase in ICP. Detrimental effects can occur when an uncontrolled increase of the ICP is not detected in time[3].

A meticulous cerebral hemodynamic control is essential to provide an adequate CPP. To do this, we systematically monitor the blood pressure invasively together with the pressure inside the endoscope, which reflexes the ICP (as long as the outflow channel of the endoscope is not partially or totally obstructed).

Though the necessity of invasive arterial blood pressure monitoring is still under discussion[1], we consider it essential for two reasons. Firstly, since it is the CPP and not the ICP that determines the CBF, both MAP and ICP are needed to evaluate the brain perfusion. Secondly,

beat-to-beat blood pressure monitoring provides the fastest method to detect the occurrence of a Cushing reflex, which is a sensitive method to identify severely impaired brain perfusion[3].

In some instances, we also use a continuous Doppler-monitoring on the medial cerebral artery for direct evaluation of the cerebral blood flow.

We report two events in one patient where severely decreased CBF, due to obstruction of the outflow channel of the endoscope, was not revealed by the ICP-readings. Both the continuous blood pressure monitoring and the Doppler-signal showed the manifest reduction of the CBF.

III2.2 Case report

A previously healthy 11 year old boy had a neuro-endoscopic biopsy of a tectum tumour. Anaesthesia was induced with propofol 2 mg/kg, remifentanil 0.1 µg/kg/min and the trachea was intubated (facilitated with cisatracurium 0.15 mg/kg). Anaesthesia was maintained with propofol 6 mg/kg/h, remifentanil 0.1 µg/kg/min, together with cisatracurium 0.15 mg/kg/h ; he was ventilated with an oxygen/air mixture (FIO_2 : 40%) to have an end-tidal CO_2 between 30 and 35 mmHg.

During the procedure we continuously monitored the arterial blood pressure using a radial artery catheter and the 'intracranial pressure' by connecting a pressure transducer to the outflow of the endoscope. The level of the foramen of Monro was used as the zero-reference point for both pressure transducers. By this, we are able to calculate the CPP reasonably accurate. We also used a bilateral transcranial Doppler onto the medial cerebral artery to assess the cerebral blood flow during the endoscopy. All the physiological data were stored on a PC for subsequent off-line analysis.

In the first 20 seconds of figure 1, we see an example of the waveforms during endoscopy when the ICP is low and there is an adequate CPP.

The Doppler signal shows the flow in the medial cerebral artery during a satisfactory CPP. After 20 seconds we see that the ICP increases moderately, while the MAP remains stable. The Doppler signal already begins to diminish. At 53 seconds, the measured ICP suddenly drops to zero. Almost immediately, a rapid drop in the Doppler signal is noticed, suggesting a total arrest of the CBF. Within 20 seconds, the arterial blood pressure curve shows a gradual but very considerable tachycardia and hypertension, indicative for the onset of a Cushing reflex, which is the result of a decreased CPP. Together with the manifest hypertension, the Doppler signal partly returns.

Based on these readings, we alerted the surgeon, who instantaneously withdrew his endoscope. Immediately, the Doppler signal and thus the CBF returned. Remarkably, after retraction of the endoscope, we can notice a clearly increased Doppler signal. The mean

amplitude of the Doppler signal in the ten seconds after endoscope retraction is at 197% of its value prior to the event.

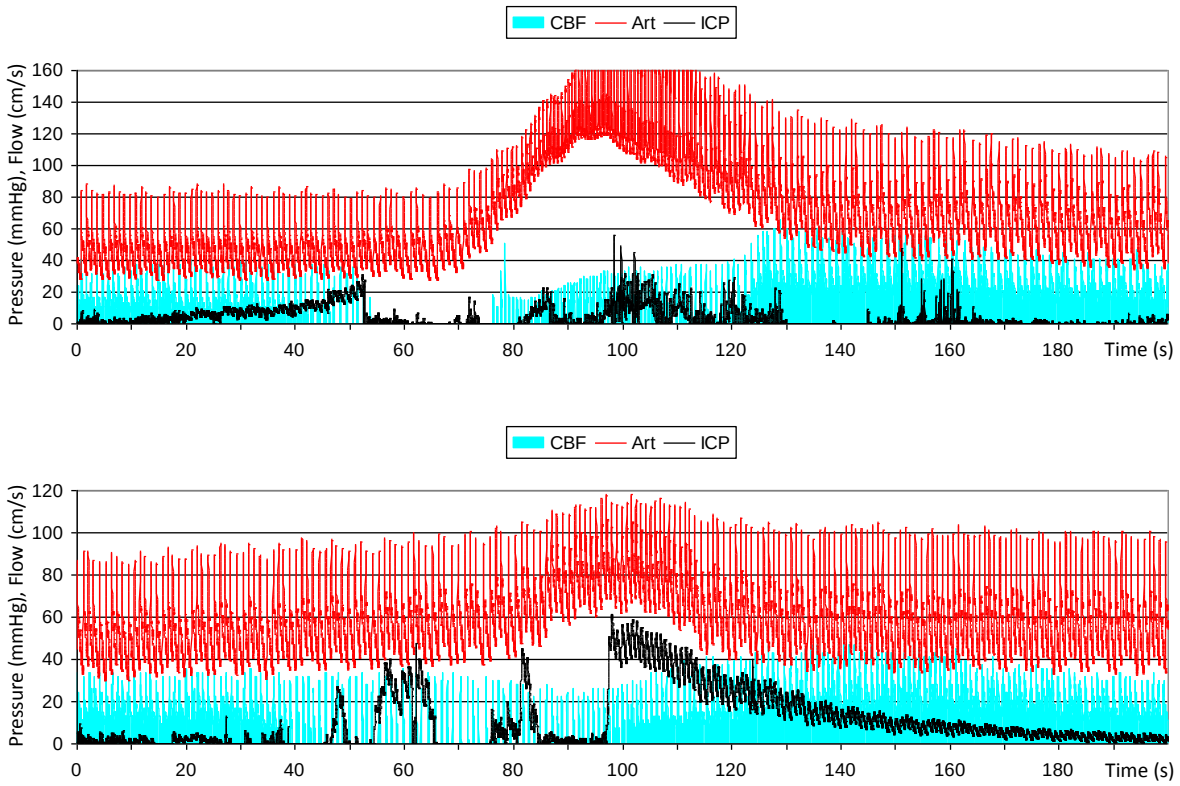

Figure 1 & 2: Unrecognised total arrest of the cerebral blood flow on conventional ICP measurement. Recordings of two events of outflow-channel obstruction during a neuro-endoscopic procedure resulting in an uncontrolled increase of the ICP, which was not detected by the ICP-monitoring. Shown are the invasive arterial blood pressure (Art, mmHg), the pressure inside the endoscope (ICP, mmHg) and the Doppler signal on the right medial cerebral artery (CBF, flow velocity). In both events, a clearly decreased Doppler signal is seen, followed by a Cushing reflex and isolated small increases in ICP-readings.

Figure 2 shows a similar event in the same patient. In the first 90 seconds, there are no clear cardiac pulsations visible on the ICP-trace. At 37 seconds, the Doppler signal starts to decrease; in particular the diastolic cerebral blood flow seems to halt, while initially the systolic velocity remains normal; the mean blood flow seems manifestly decreased. The absence of a pulsatile ICP-waveform suggests inadequate registration of the ICP. Although the ICP-waveform shows very brief peak-pressures of 60 mmHg at 60 seconds and at 80 seconds, the numeric representation of the ICP on the anaesthesia monitor did not mention an unusual increase of the ICP. At around 60 seconds, the MAP starts to increase progressively; at 90 seconds, a tachycardia develops. At 97 seconds, suddenly a pulsatile ICP waveform reappears, showing a mean ICP of 50 mmHg. In the seconds following the reappearance of the ICP-pulsations the ICP decreases spontaneously, followed by a normalisation of the blood pressure and Doppler signal.

In both cases, over a few minutes after restoration of the CBF, the blood pressure and heart rate returned to their initial values. The patient awoke in the operating room and was discharged from hospital 3 days later with no complications.

III2.3 Discussion

The anaesthesiologic work-out for neuro-endoscopic procedures considering the preservation of the CPP remains controversial. The necessity of invasive blood pressure monitoring during neuro-endoscopy is questioned because measuring the pressure inside the endoscope is assumed to be an adequate alternative[1]. Although in most cases this is correct, high flush-rates or intra-endoscopic obstruction of the outflow may make this method of assessing the ICP inaccurate. We present a patient having a neuro-endoscopic procedure where the measured pressure inside the endoscope strongly underestimated the actual ICP.

At the moment of the obviously false ICP-readings, there was a lot of debris floating in the rinsing fluid. Almost certainly, the events were caused by an obstruction of the outflow channel inside the endoscope, which prevented the normal evacuation of the rinsing fluid and caused an inadequate ICP assessment.

In the first event (figure 1), an obstruction of the outflow channel caused a total arrest of the CBF, illustrated by a disappearance of the Doppler signal and an unmistakable onset of a Cushing reflex. The significantly increased CBF observed after restoration of the ICP is very suggestive for a post-ischemic hyperaemia.

In the second event (figure 2), after the reappearance of the pulsatile ICP-waveform, and thus presumably a restoration of the free outflow, we can see a spontaneous normalisation of the ICP, blood pressure and CBF. In this event, the problem was only noticed after the ICP was returning to safe values, so no intervention was done.

In both events, the Doppler signal clearly indicates that the CBF was decreased very significantly while the ICP remained modest.

Although a meticulous observation of the ICP-waveform could have alerted the anaesthesiologist that something unusual was happening, it would most probably not have been noticed purely relying on the routine ICP-readings. Indeed, the routine monitor did not show at any moment an ICP increase above 20 mmHg.

Although the manifest tachycardia could have been seen on the ECG, a tachycardia can be produced by a multitude of causes and the "normal" ICP values would only have misled the anaesthesiologist. In both events, the small increase in ICP readings would not have been considered worrisome in the absence of a Cushing reflex notification. Consequently, deleterious events were avoided, because the anaesthetist relied on the onset of a Cushing reflex, and not on an increase of the ICP. The abrupt disappearance of the Doppler signal

together with the low-ICP readings made us assume the Doppler probes were dislocated. Only after the appearance of the Cushing reflex, we became aware of the problem.

Therefore, in contrast to the statement made by Fabregas and Craen[1, 2], we would like to conclude that continuous invasive blood pressure monitoring is essential during every neuro-endoscopic procedure where an iatrogenic increase of the intracranial pressure is possible. A continuous monitoring of the pressure inside the endoscope is not a safe alternative for continuous invasive blood pressure monitoring. Moreover, even if the ICP-measurement is reliable, it is not the ICP value on itself, which is important, but a low CPP[3]. This is another compelling reason to measure the MAP invasively beat to beat during a neuro-endoscopic procedure.

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3

III3 Endoscopic pressure detection assembly

EP 2 598 015 B1

EUROPEAN PATENT SPECIFICATION

Adapted from : "Endoscopic Pressure Assembly"
Date of publication and mention of the grant of the patent: 03.09.2014
Inventors : F Dewaele, AF Kalmar, B Blanckaert, C Mabilde

III3.1 Field of the invention

The present invention relates to a pressure detection assembly for determining pressure in a tissue cavity inspected by an endoscope.

III3.2 Background of the invention

Endoscopy is employed in many surgical procedures such as neurosurgery, transurethral resection of the prostate/bladder, and many other procedures. In such procedures, a continuous flow endoscope is frequently used.

Briefly, a continuous flow endoscope is adapted to allow rinse fluid simultaneously to enter and escape from a tissue cavity *via* separate entry and exit points. It was initially assumed that an open outlet channel would prevent a rapid build-up of pressure within the tissue cavity. However, in practice, detached tissue pieces, larger than a critical size, present in the tissue cavity are unable to pass through the rinse outlet port leading to obstruction of the outflow channel which can provide an erroneous pressure reading, and pressure-build up.

There is thus a need for dynamic pressure assessment that is clinically feasible to implement, which provides a more accurate measurement of actual pressure in the ventricle, can be applied easily aseptically and avoids the problems associated with blockages.

III3.3 Summary of the invention

The embodiment of the invention is a pressure detection assembly adapted for use with a continuous flow endoscope. Its couplings provides a water impermeable seal to the rinsing inlet of the endoscope, configured for convenient advancement into the rinse lumen towards the distal tip. The outer diameter of the elongated tubular member is adapted to permit passage of rinsing fluid without substantial hindrance to the flow.

The assembly provides a measurement of ambient pressure at the distal end of the endoscope that accurately reflects the pressure in the cavity of the intervention while the endoscope is rinsing.

A particular clinical advantage consists of the possibility for exquisitely control of the intracranial pressure by using a closed-loop (feedback loop) system comprising pumps and/or valves and a controller to maintain pressure at the predefined level. The closed loop system may be advantageously employed to deliberately increase pressure at the intervention site, which pressure increase expedites clot formation in the case of a haemorrhage.

The catheter can be made a disposable item, overcoming any problems of sterilisation. The assembly provides an economical solution to the problem, that can be deployed on existing endoscopes without significant adaptation.

III3.4 Further reading

See appendix 2 for a more detailed description of the patent.

4

III4 Pressure monitoring during neuroendoscopy: new insights

Br J Anaesth. 2011 Aug;107(2):218-24.

Kalmar AF, Dewaele F, Van Canneyt K, Vereecke H, Absalom A, Caemaert J, Struys MM, Van Roost D.

III4.1 Abstract

Background: Significant increases in intracranial pressure (ICP) may occur during neuroendoscopic procedures. To detect and prevent serious and sustained increases, ICP should be monitored. At present, controversy exists on the optimal location of the monitoring sensor. Therefore, we conducted an in vitro study to estimate the pressure gradients between the ventricle, the 'gold standard' site, and the rinsing inlet and outlet.

Methods: A head model and a standard endoscope were used. Rinsing was enforced by using a pressurized infusion bag. Using clinically relevant flow rates, pressure was measured at the rinsing inlet and outlet, in the ventricle, and at the distal end of the rinsing channel using a tip sensor or a capillary tube.

Results: At a flow of 61 ml min^{-1}, the steady-state pressures measured at the rinsing inlet, in the ventricle, and at the rinsing outlet were 38, 26, and 12 mm Hg, respectively. At 135 ml min^{-1}, these increased to 136, 89, and 42 mm Hg. Transendoscopic pressure measurements were always within 1 mm Hg of the ventricular pressure.

Conclusions: During endoscopy, measurements at the rinsing inlet overestimated the ventricular pressure by ~50 mm Hg during heavy rinsing, whereas measurements at the rinsing outlet underestimated the pressure by ~50 mm Hg. An electronic tip sensor or a pressure capillary tube placed at the distal end of the lumen of the rinsing channel of the endoscope did not interfere with rinsing flow and produced measurements that were equal to ventricular pressures.

III4.2 Introduction

During the past 3 decades, there has been renewed interest in neuroendoscopy,[1–6] such that endoscopic intraventricular procedures are common in most neurosurgical departments.

During these procedures, there is a need for continuous rinsing of the ventricular cavities. Initially, it was assumed that an open outflow channel would prevent a rapid build-up of intracranial pressure (ICP). However, many publications have shown that significant increases in ICP may still arise during these procedures. The principal reasons for induced intracranial hypertension are high flow rinsing (used to improve visibility during bleeding[7] or to maintain access in collapsing ventricles)[8] and obstruction of the outflow channel by tissue debris,[9] blood clots,[10] or kinking of the outflow tubes. Excessive increases in ICP should be avoided, since intracranial hypertension can lead to cardiovascular complications,[11 12] herniation syndromes, retinal bleeding,[8 10] and excessive fluid resorption.[13]

Transcranial Doppler ultrasonography measurements during rinsing procedures have shown severe decreases in cerebral perfusion without systemic haemodynamic warning signs.[14] ICP monitoring is thus important, but the optimal location of monitoring is controversial. Although direct measurement of ventricular pressure is the gold standard, insertion of a separate ventricular catheter for this purpose is clinically impractical and difficult to justify. Since fluids flow down pressure gradients, and flowing fluids generate pressure gradients, measurement at the rinsing inlet and outlet is likely to correlate poorly with ventricular measurements. Pressure measurements at the inlet and outlet can only provide valid estimations of the ventricular pressure when there is no flow (i.e. if the rinsing inlet and outlet are closed simultaneously, and pressures are measured after a suitable interval to allow for equilibration of pressures). This is seldom clinically practical, and it is especially impractical when high rinsing flows are required because of brisk bleeding.

Our goal is to be able to perform accurate dynamic ICP assessments without the need for additional invasive procedures such as ventricular catheter insertion. In order to investigate the significance of the dynamic pressure gradients across an endoscope, we have compared measured pressure readings taken at the rinsing inlet and outlet with those measured via a separate ventricular catheter in a realistic head model using standard endoscopes and clinically relevant rinsing fluid flow rates. Additionally, we have developed a transendoscopic method of pressure measurement at the distal end of the endoscope through the irrigating

lumen, and have compared pressures measured at this site with those measured in the ventricle and at the rinsing inlet and outlet.

III4.3 Methods

III4.3.1 Experimental set-up

A custom-made polypropylene head model (internal volume 2900 ml) was used for the in vitro measurements (Fig. 1). It was completely filled with 0.9% saline solution and sealed hermetically. A pre-coronal burr hole was made and closed with a rubber seal. A Caemaert endoscope (Richard Wolf, Knittlingen, Germany) was installed through the seal and fixated with a pneumatic holding device (Aesculap, Tuttlingen, Germany). The rinsing inflow and outflow channels of the endoscope have an internal diameter of 1.67 mm and a length of 350 mm. A second burr hole was made and sealed with a rubber seal. A standard external ventricular drain with an internal diameter of 1.3 mm (Integra NeuroSciences, Plainsboro, NJ, USA) was positioned through the seal into the fluid-filled cavity. The rinsing system was installed in the standard manner for neuroendoscopic procedures: three-way stop cocks (Discofix, B. Braun, Melsungen, Germany) were connected at the rinsing inlet and at the rinsing outlet for pressure measurement (Fig. 1). Pressure transducers (PMSET 1DT-XX Becton Dickinson Critical Care Systems Pte Ltd, Singapore) were connected to the three-way stopcock and to the ventricular catheter via low compliance pressure tubing.

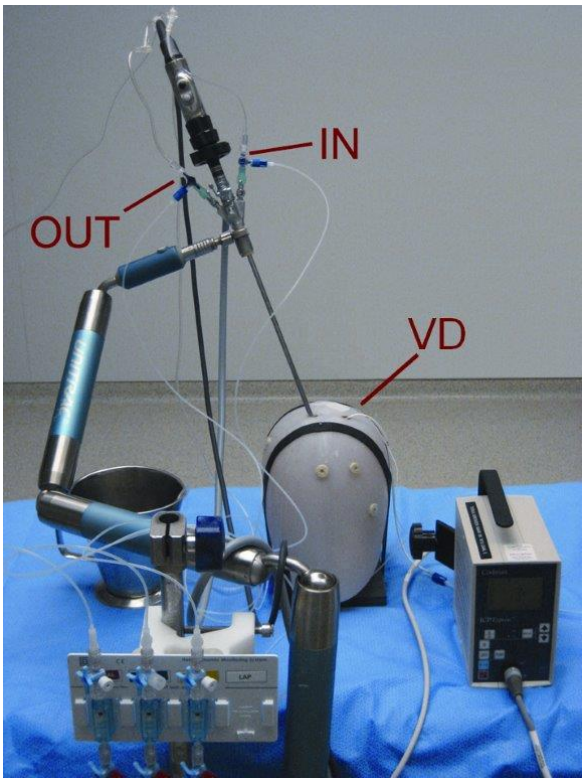

Figure 1: Overview of the experimental set-up during the first measurement: a head model filled with 0.9% saline, the Caemaert endoscope with a pneumatic holding device, and pressure measurements at the level of the rinsing inlet (IN), the rinsing outlet (OUT), and through a ventricular drain (VD). The Codman unit is used in the next measurement.

All pressure transducers were flushed with saline, and zeroed at the level of the external acoustic meatus.

The irrigation system was installed as per routine clinical practice: a pressurized flush bag of 0.9% saline was connected to the valve at the rinsing inflow of the endoscope via an infusion set with a standard flow regulator. The bag was placed under a constant pressure of 300 mm Hg using a Ranger Pressure Infusion System (Arizant Inc., MN, USA).

An intravenous infusion set (Intrafix Primeline I.S., B.Braun, Melsungen, Germany) was used as an outflow tube. The luer lock was connected to the three-way stopcock at the rinsing outlet of the endoscope, and the opposite end was positioned at the level of the burr hole. For precise determination of the flow rate during pressure measurements, the effluent was collected into an accurate measuring glass for exactly 60 s.

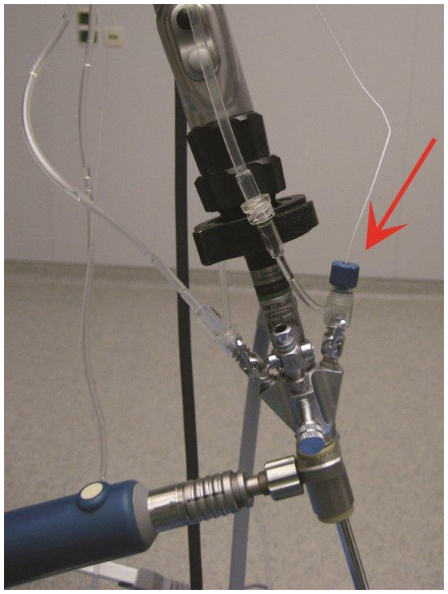

Figure 2: Depiction of the solution in which an ICP tip sensor (arrow) is introduced through the rinsing inlet channel as far as the tip of the endoscope in order to measure static pressures.

All pressure transducers were connected to an S5 monitor (GE Health Care, Helsinki, Finland) which displayed the analogue pressure waveforms in real time, digitized the signals at a sampling frequency of 100 Hz, and transmitted them to a PC for electronic storage using S5 collect software (GE Health Care).

III4.3.2 Measurements

Four separate experiments were performed. At the start of each experiment, the endoscope was introduced into the ventricular cavities and a rinsing flow, set at 'fast dripping speed', was initiated, as per routine clinical practice. After baseline pressure measurements had been recorded, the flow rate was increased in small increments, using the flow regulator, until a flow of 210 ml min^{-1} was reached. After each change in flow, an equilibration time was observed until a steady plateau pressure was reached. For each flow rate, the plateau pressure was recorded.

Measurement 1

The ventricular pressures were measured (via the ventricular catheter) and compared with the pressures measured at the rinsing inlet and rinsing outlet.

Measurement 2

In a second step, the equipment set-up was modified to enable pressures to be measured at the distal end of the lumen of the endoscope. A connecting piece (Rotating Male Hub Tuohy

Borst with Sideport nr 80346, Qosina, Edgewood, NY, USA) was attached to the endoscope, and a Codman MicroSensor^{TM} ICP tip sensor (Johnson & Johnson Professional, Raynham, MA, USA) was introduced through the rinsing channel and advanced, so that it was located 1 mm proximal to the distal end of the endoscope (Fig. 2). The tip sensor was also connected to the S5 monitor. The pressures it recorded were then compared with the pressure in the ventricle and at the rinsing outlet.

Measurement 3

The second protocol was repeated but instead of the Codman tip sensor, a polyimide pressure capillary tube was used. Using the same leak-proof connecting piece, the catheter was slid through the rinsing inflow channel until the tip was 1 mm proximal to the distal end of the endoscope.

Measurement 4

The first measurement protocol was repeated but with a short Caemaert endoscope. This endoscope also has a rinsing channel diameter of 1.67 mm, but a shaft length of 240 mm (as opposed to 350 mm in the standard instrument).

III4.3.3 Data analysis

In the subsequent analysis, for each flow, the steady-state pressures at the different measuring points were graphically represented. The relationship between flow and pressure was determined by linear regression. The difference between the pressure in the ventricle - which is considered the gold standard - and the other pressure measurement sites was calculated for each flow rate.

The Reynolds number was calculated for each flow rate to evaluate whether laminar flow was likely. For each flow rate, at which laminar flow was likely (up to 180 ml min^{-1}), the measured pressure gradients were compared with pressure gradients predicted by the Hagen–Poiseuille equation: $\Delta P=8\mu LQ/\pi r^4$.

Data were normally distributed and are presented as mean.

III4.4 Results

The evolution of the ventricular pressure during initiation of rinsing is shown in Figure 3. Before the rinsing was started, a ventricular pressure of 8 mm Hg was observed. At a flow of 85 ml min^{-1}, a peak pressure of 51 mm Hg was reached, before the pressure stabilized at 18 mm Hg.

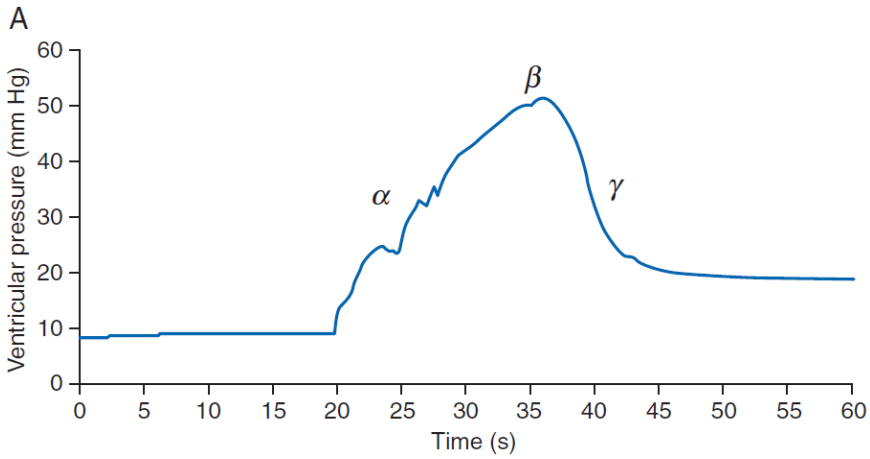

Figure 3A: Results of the first measurement. Evolution of the pressure, measured through the ventricular drain, during initiation of the rinsing process at a 'fast dripping speed' of 85 ml min^{-1}. The pressure increases (α) from a baseline pressure of 8 mm Hg to a peak pressure of 51 mm Hg (β), and equalizes at 18 mm Hg after the siphoning effect (γ) of the outflow tube has taken place.

Figure 4 shows that when the rinsing flow was suddenly increased from a stable 40–185 ml min^{-1}, the ventricular pressure increased from 25 to 122 mm Hg, while the pressure at the inlet increased from 42 to 223 mm Hg and the pressure at the outlet increased from 9 to 53 mm Hg.

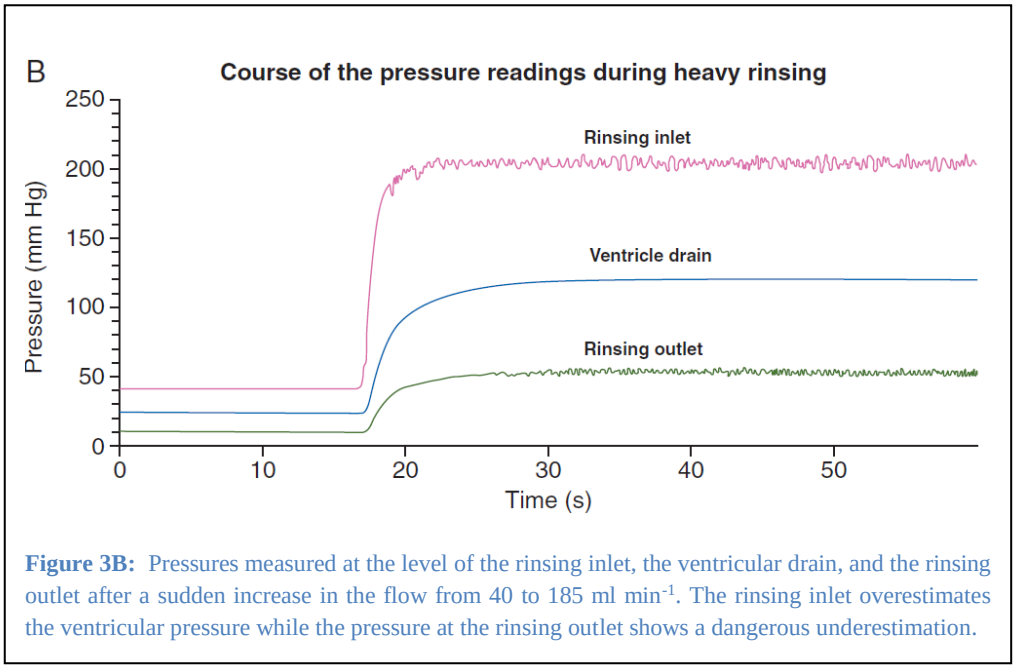

Figure 3B: Pressures measured at the level of the rinsing inlet, the ventricular drain, and the rinsing outlet after a sudden increase in the flow from 40 to 185 ml min^{-1}. The rinsing inlet overestimates the ventricular pressure while the pressure at the rinsing outlet shows a dangerous underestimation.

The pressure measured at the different points in relation to the flow is represented in Figures 3C and 4.

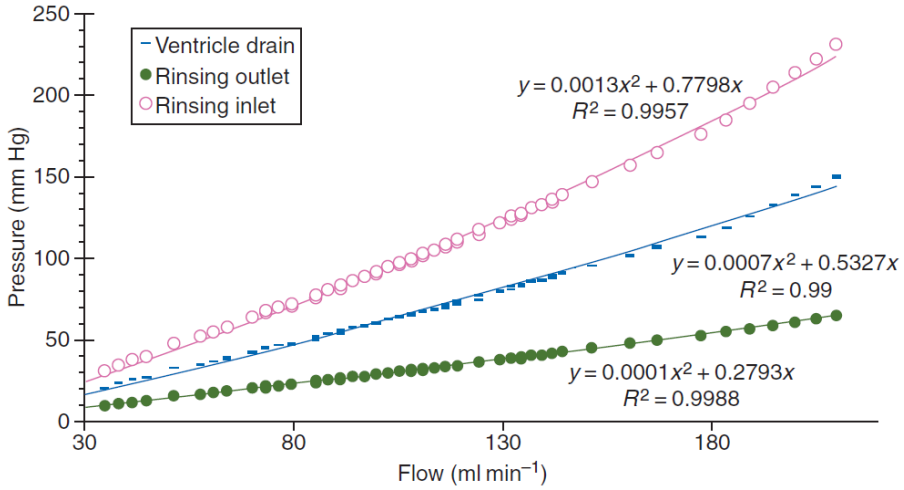

Figure 3C: The same pressures as figure 3B, but a function of the flow (ml min-1).

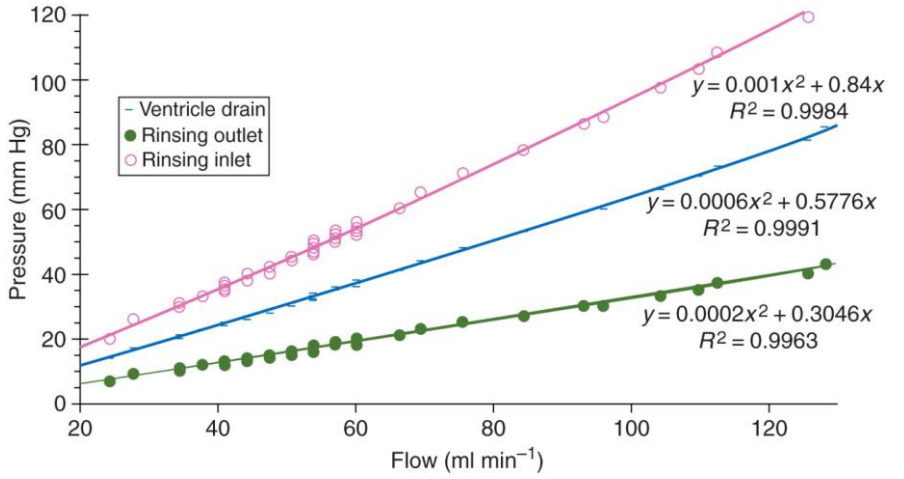

Figure 4: Results of the fourth measurement. The pressures measured over the short Caemaert endoscope are analogous to the results of the first measurement.

The pressure gradients between the rinsing inlet, intraventricular, and rinsing outlet related to the flow are shown in Figure 3C. At a flow of 42 ml min^{-1}, the measured pressures are 38, 26, and 12 mm Hg, respectively. At a flow of 135 ml min^{-1}, the pressure increased to 136, 89, and 42 mm Hg, respectively.

Both the Codman tip sensor and the capillary tube measurement showed a maximal inaccuracy of 21 to 1 mm Hg at any flow (Fig. 5A and B).

The short Caemaert endoscope (Fig. 4) showed a similar evolution of the pressure gradient between the rinsing inlet, intraventricular, and rinsing outlet. At a flow of 24 ml min^{-1}, the measured pressures were 20, 14, and 7 mm Hg, respectively. At a flow of 148 ml min^{-1}, the pressures increased to 146, 99, and 49 mm Hg, respectively (Fig. 4).

The Reynolds number, calculated for the dimension of the endoscope, is 663 at a flow of 50 ml min^{-1} and 2650 at a flow of 200 ml min^{-1}. At a flow of 61 ml min^{-1}, the measured pressure gradients between the rinsing inlet, ventricle, and rinsing outlet were 18 and 19 mm Hg, respectively, while the theoretical pressure gradient, calculated by Poiseuille's equation was 17 mm Hg. At a flow of 130 ml min^{-1}, the measured pressure gradients were 31 and 31mmHg; the calculated was 27 mm Hg. At a flow rate of 210 ml min^{-1}, the measured pressure gradients were 81 and 85 mm Hg, while the calculated gradient was 57 mm Hg.

III4.5 Discussion

During endoscopic neurosurgery, significant intracranial hypertension may occur during rinsing of the ventricular cavities. As this may cause severe complications, accurate monitoring of ICP is essential. To the best of our knowledge, the optimal location and method for monitoring ICP during endoscopic neurosurgery has not been determined.

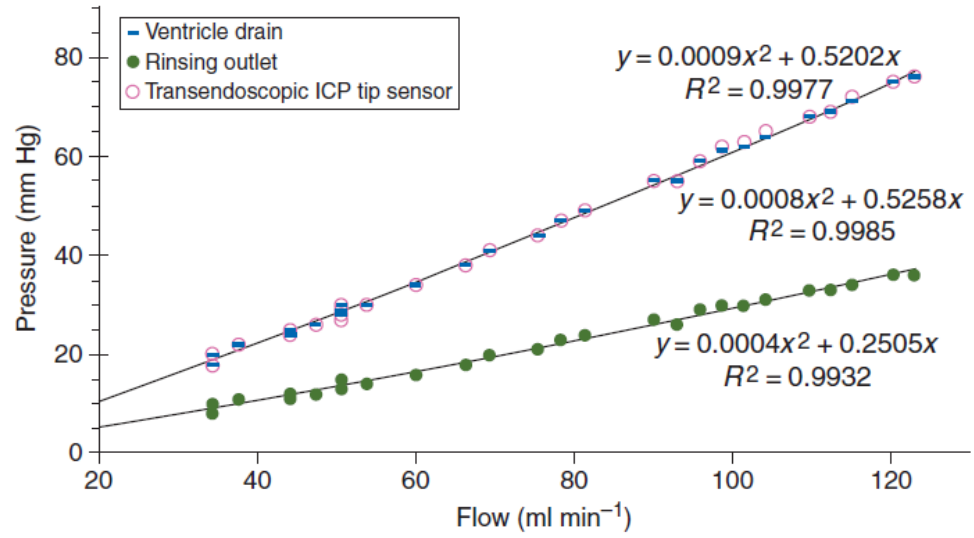

Figure 5A: Results of the second measurement. The pressures measured by the ICP tip sensor at the tip of the endoscope are exactly the same as those of the ventricular drain, the gold standard. The pressure measured at the rinsing outlet severely underestimates the ventricular pressure.

ICP measurements with an ICP tip sensor through the working channel have been proposed, but this may interfere with the surgical procedure.[15] An intra-parenchymal ICP tip sensor will provide reliable measurements, but it is invasive and therefore less acceptable as a routine practice.[16]

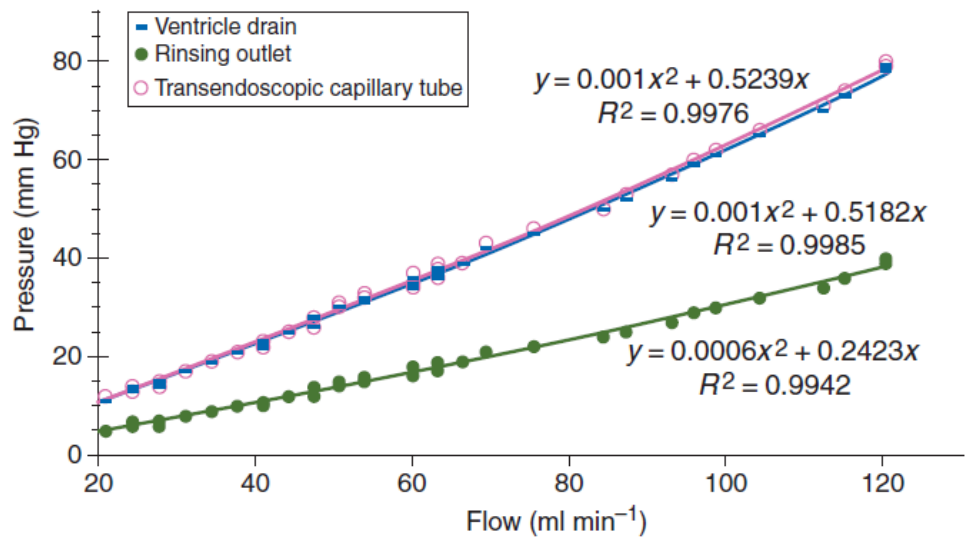

Figure 5B: Results of the third measurement. The pressures measured by the capillary tube at the tip of the endoscope are exactly the same as those of the ventricular drain, the gold standard.

An epidurally placed ICP tip sensor is a less invasive, but a less reliable method.[17] Moreover, in a recent study,[18] comparing epidural pressures (measured with an electronic ICP tip sensor) with those measured at the endoscopic rinsing inlet, epidural pressures were found to be consistently higher than the inflow pressures. This result, which is counter-intuitive, suggests that the epidural space is a poor choice of location for estimating ICP.

Although considered the gold standard, pressure measurement via a separately inserted ventricular catheter is generally unfeasible and difficult to justify. At the same time, measurements at the rinsing inlet and the rinsing outlet are unlikely to accurately reflect ventricular or ICP.

We therefore constructed a head model, to assess the likely significance of these pressure gradients and to assess the accuracy of a novel technique to measure pressures at the distal end of the endoscopic lumen.

After initiation of rinsing, the pressure changes witnessed in the ventricle of our head model (Fig. 3A) illustrate, first, the importance of using an outflow tube and, secondly, the importance of correct positioning of the distal end of the outflow tube. After initiation of rinsing (flow 30 ml min^{-1}) in our model, only a transient period of intracranial hypertension was observed. The evolution of ventricular pressure changes during this period showed four phases (Fig. 3A).

During the first phase, pressures increased as the endoscope and the tubing filled with rinsing fluid (Fig. 3A, a), until reaching a peak of 51 mm Hg (Fig. 3A, b). After the onset of the siphoning effect of the outflow tube, the ventricular pressure declined (Fig. 3A, g), until the ventricular pressure settled at 18 mm Hg, at which point the siphoning effect balanced the

hydrostatic pressure. If the distal end of the outflow tube is obstructed, absent, or at an incorrect level, a continuously elevated ICP will be induced by the hydrostatic pressure in the outflow channel. The total ICP will be the sum of the hydrostatic pressure and the pressure build-up caused by impedance in the outflow channel. Conversely, if the distal end of the outflow tube is located too low, the siphoning effect will cause a collapse of the ventricles.

Increasing the rinsing flow resulted in a considerable increase in the pressure at all sites. In measurement 1, there were significant differences in pressure readings at the different locations. Monitoring at the rinsing inlet overestimated the ventricular pressure by 12 mm Hg when the flow rate was 42 ml min^{-1}, and by 81 mm Hg at a flow rate of 210 ml min^{-1}. On the other hand, monitoring at the rinsing outlet underestimated the ventricular pressure by 14 mm Hg at 42 ml min^{-1} and by 85 mm Hg at 210 ml min^{-1}. Similar differences were found with the short endoscope - an overestimate of ~41 mm Hg and an underestimate of ˜ 42 mm Hg at the inlet and outlet ports at a flow rate of 128 ml min^{-1}. This pressure difference is caused by the dynamic resistance in the rinsing channel, and correlates well with the pressure gradients predicted by the Hagen–Poiseuille law (difference of 1–2 mm Hg at 61 ml min^{-1} increasing to 7–8 mm Hg at 130 ml min^{-1}).

Transendoscopic monitoring of the pressure at the distal tip of the endoscope using an electronic Codman ICP tip sensor provided a very accurate assessment of the ventricular pressure (and thus of the ICP). Of course, the application of an extra monitoring device and the use of a disposable electronic ICP tip sensor introduce some practical and financial considerations. In order to find a cheaper and more practical method of transendoscopic pressure monitoring, we replaced the tip sensor with a fluid-filled capillary tube connected to a standard pressure transducer outside the head. The tip of the catheter was placed at the same location as the tip sensor (1 mm proximal to the distal end of the endoscope). With this capillary tube, the transendoscopic pressure measurements compared very favourably with ventricular pressure measurements (maximal error of +1 mm Hg).

Since this pressure capillary tube partially obstructs the rinsing inflow channel, a reduction in rinsing capacity is expected. During the in vitro analysis, a decrease of only 17 ml min^{-1} was observed during heavy rinsing after introduction of the pressure capillary tube.

Because induced intracranial hypertension only becomes clinically relevant at faster rinsing flow rates - above 50 ml min^{-1} - and the rinsing flow is relatively stable, the compliance of the intracranial system is of minimal influence on the observed pressure values. On the basis of the Monro-Kellie hypothesis[19] - that with an intact skull, the sum of the volumes of the brain, the cerebrospinal fluid, and the intracranial blood is constant - the capacity for expansion of the intraventricular volume during fast rinsing flow rates is limited to the intracranial blood volume. During gradual increase in flow rate, the induced blood volume displacement caused by changes in rinsing pressure is minimal compared with rinsing volumes. In our model, the pressure waveform stabilizes almost immediately after adjustment of the rinsing speed. Nevertheless, when the pressure is increased rapidly and severely (Fig. 3B), it takes several seconds before stable pressure readings are observed.

Our study has several limitations. The findings are by nature specific to the materials and equipment used. Our conclusions are based on a set-up of enforced rinsing with pressure infusion bags; this is not universally practised. However, even set-ups using passive rinsing remain vulnerable to obstructed outflows. Secondly, the rinsing channel of the endoscope we used has a small internal diameter. Pressure gradients will be lower with endoscopes with larger channels, while endoscopes with narrower rinsing channels will show even greater pressure gradients. An example of the latter is the MINOP Ventriculoscope (Aesculap, Tuttlingen, Germany) in which the diameter of the rinsing channels is 1.4 mm.

Thirdly, in this experimental set-up, there was no tissue debris, which is common in clinical practise, and which will increase further the gradient between ventricular and outlet pressures. If debris completely obstructs outflow, then of course the outflow measurement has no correlation with ventricular pressure and will severely underestimate it.

Finally, the outflow of rinsing fluid around the endoscope via the burr hole and escape via the working channel were prevented in this study.

In conclusion, the findings of this laboratory-based assessment suggest that clinically significant pressure gradients across the endoscope are generated during rinsing despite an open outflow tract. These gradients are generated by dynamic resistances in the rinsing channels (Poiseuille's law). Measurement at the rinsing inlet gives a severe overestimate of the true ICP (up to 50 mm Hg) and if clinicians were to respond to these pressures, this would unnecessarily impede the rinsing efforts of the surgeon. Reliance on measurements at the outflow point, which provides systematic severe underestimates of the true ICP (up to 50 mm Hg), will delay crucial intervention. Transendoscopic measurement of the pressure at the distal end of the endoscope accurately reflects ventricular pressure. There was no significant difference in the pressure measured at the tip of the endoscope using a Codman ICP tip sensor and a pressure capillary tube. The use of a small pressure capillary tube in the rinsing inlet channel has no significant influence on the rinsing capacity. Since complications are even reported during a straightforward ETV (Endoscopic Third Ventriculostomy), we have to recommend pressure monitoring during every endoscopic procedure.

Conflict of interest

A patent application was filed.

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IV

Reversible upgrading of central-venous catheter lumina

1

IV1 Central venous access and pressure monitoring

In many medical conditions, a catheter is inserted in a peripheral vein (the jugular vein, the subclavian vein or the femoral vein) and advanced in order to locate the distal end of the catheter in central venous system. (= close to the heart). It is used to administer medication or fluids, obtain blood tests, and measure central venous pressure.

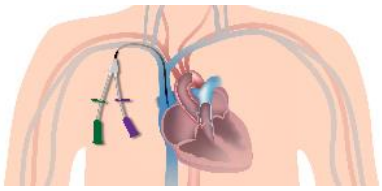

Figure 1: Central venous catheter with distal tip in the vena cava superior.

IV1.1 Procedure of central-venous catheter placement

The skin is cleaned, a hollow needle is advanced through the skin until blood is aspirated, and the line is then inserted using the Seldinger technique: a blunt guidewire is passed through the needle, then the needle is removed, and the central line itself is then passed over the guidewire, which is then removed. This procedure involves several medical risks, is unpleasant for the patient, and is time consuming.

IV1.2 Single-lumen versus multilumen central venous catheters

Central venous catheters exist with a single lumen up to 5 lumina. This allows for different medications to be administered independently, without mixing, and to do simultaneous fluid administration and accurate pressure measurement. A particular disadvantage of multilumen catheters is that the internal diameter of the different

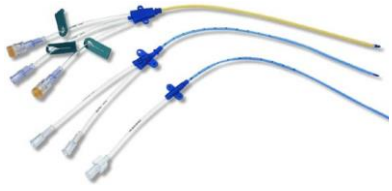

Figure 2: single, dual en triple lumen central venous catheter.

lumina decreases significantly.

The outside of any catheter is soft in order to be minimally traumatic in respect of endothelium damage due to insertion and cardiac pulsations. Standard multichannel catheters are made from a solid tube of a single material, into which individual channels are left open. As a result, the internal channel walls are relatively thick, and the catheter is stiffer compared with a single lumen device. Moreover, there is a loss of available lumen area. (figure 3).

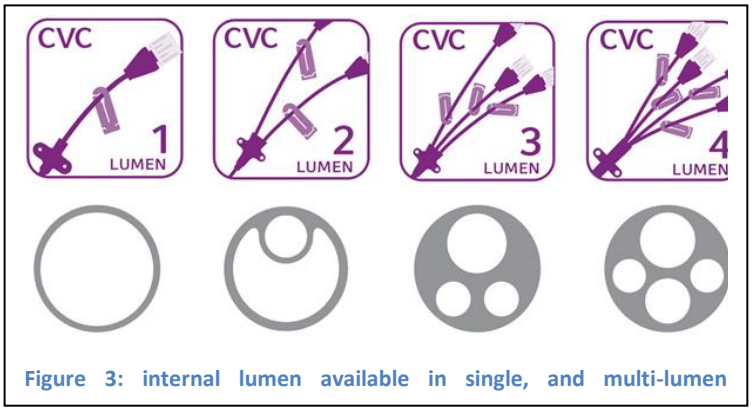

Figure 3: internal lumen available in single, and multi-lumen

If the interior additional channels were to be made from a different material with more convenient stiffness, thinner walled catheters can be used.

The presence of multiple lumina, especially when they are not in active use anymore, increases the risk of severe complications – such as infections or thrombotic events – very significantly. The American guidelines from the CDC[1] therefore prescribe to use the minimal number of lumina necessary. During the course of a hospitalisation the need for separate lumina and separate pressure measurement changes depending on the evolution of the condition of the patient, but at this moment, switching the number of lumina has many disadvantages, and therefore most patients have a needlessly high number of lumina for a large period of time.

In addition, because a single lumen catheter, by virtue of its more elastic outer wall, is less harmful for the endovascular tissue, a single lumen catheter is to be preferred if possible: a more flexible catheter reduces endothelium damage and consequently thrombosis and emboli. Moreover, single lumen catheters have a more advantageous cross-sectional area for a given outer diameter, which is important when a high rate of fluid administration is required.

A convenient and safe switching to more or less channels would therefore be advantageous.

IV1.3 Complications in central-venous catheter (re)placement

In most cases, the procedure is minimally traumatic. Still, it can give rise to complications such as pneumothorax, hematothorax, nerve damage, accidental puncture of arteries, and stroke. During the period of hospitalisation, the needed number of lumina often changes according to the medical circumstances. Conventional methods of swapping a single lumen catheter for a multi-lumen catheter entails several risks: the existing catheter is often removed on a guidewire, and the replacement catheter is fed on this guidewire. Driving a new sterile catheter through the colonised tissues involves a significantly increased risk of infection, especially in patients with a weakened immunity. Therefore, in most cases the practitioner

may perform an entirely new puncture, but this strategy involves all the risks of the first placement.

IV1.4 Presented solution for flexible lumen number adaptation

Based on the device we developed for accurate and convenient intracranial pressure measurement during neuro endoscopy, we made several prototype for easy upgrading of a single-lumen catheter to a multilumen catheter. Three major requirements must be set before any clinical application:

1. Acceptable flow on all channels
2. Guaranteed sterility and biocompatibility
3. Easy and safe use in clinical practice, with fluent introduction in the main catheter.

After several iterations, a device was developed which addresses these requirement.

The straightforward conversion from a single-lumen to a multi-lumen or vice versa catheter decreases the number of manipulations, increases patient comfort, reduces infection risk, and risk of other complications. The cost of the procedure is also reduced because the need for the more expensive multilumen catheters is obviated, and more importantly, the time-consuming procedure of catheter replacement is avoided.

We propose the use of a soft and flexible single lumen catheter, that can be later upgraded to a multi-lumen catheter using stiffer materials. Since the initial catheter is generally single lumen, it may be soft and, therefore, avoids trauma to the endothelium. Any rigidity of the later-inserted capillary tube will not cause damage the endothelium because it is introduced within the lumen of the initial catheter. It thus provides a different material choice for the internal lumina and external catheters. This allows for optimal use of soft material for the outer catheter, and the use of ultrathin walled rigid material for the internal capillary system.

The use of different material for the additional lumen has a further advantage in that the capillary tube may be optimized for pressure measurements. For optimal transduction of a pressure change, rigid tubing material is preferred.

A further use of requirement for multichannel catheters is the necessity to have a lumen that is exclusively used for a particular drug. Because of the high pharmacological activity and short half-life of certain drugs (for instance adrenaline), it is critical that its administration is uninterrupted and constant. If the drug would be administered through the main catheter channel, an interruption of the flow due to an empty fluid canister or a kink, the interruption of the drug administration and the subsequent overdose of drug after restoration of the fluid flow would be unacceptable. Secondly, when using a dedicated lumen for the drug, changes in drug administration have immediate pharmacological effect, while mixing it with the main channel may delay its effect. Another reason for administering drugs in separate channels is

pharmacological incompatibility, which means certain drugs cannot be mixed before dilution in the blood.

Introduction of a capillary into an invasive tube such as venous catheter or central venous catheter and fixation of the adaptor to the coupling of such invasive tube is ideally performed under sterile conditions to prevent infections. It may be challenging for a practitioner to introduce the flexible capillary tube shaft into the proximal part of the invasive tube coupling without touching the sterile parts.

Accordingly an applicator package, comprising the capillary tube assembly as described herein and an applicator was developed. The applicator and applicator package allow the sterile introduction of the capillary tube shaft into the invasive tube lumen.

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2

IV2 Capillary Tube Assembly

United States Patent

(10) **Patent No.: US 8,882,716 B2**
(45) **Date of Patent: Nov. 11, 2014**

Adapted from : "Capillary Tube Assembly"
Date of publication and mention of the grant of the patent: 11.11.2014
Inventors : F Dewaele, AF Kalmar, B Blanckaert, C Mabilde

IV2.1 Field of the invention

The present invention relates to the field of invasive medical tubing, more specifically to catheters and lumbar puncture needles.

IV2.2 Summary of some aspects of the invention

IV2.2.1 Application for central venous catheters

One application relates to a detachable device for adding one or more channels to the central venous catheter (CVC). It relates to the capillary tubes for increasing the number of lumina, the adaptor, intermediate coupling and the applicator (figure 1). The thin walled capillary tube permits addition of lumina with minimal obstruction of the main channel.

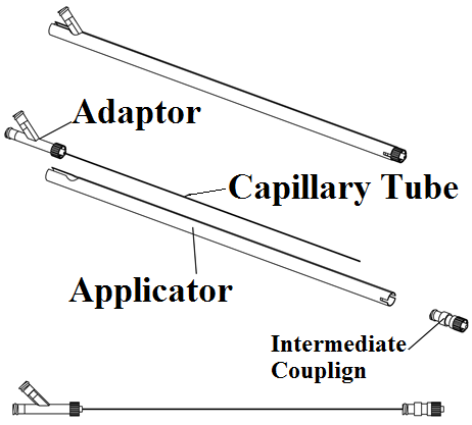

Figure 1: General architecture of the capillary tube assembly

The additional channel may be employed as a hydrostatic pressure detector, for measuring the pressure at the distal tip of the invasive tube.

The capillary tube assembly allows one channel of the catheter to have separate pressure measurement and drug delivery functions, without sacrificing accuracy of the CVP measurement.

In the next chapter, an elaborate description will be provided of a prototype of a medical device developed for convenient and reversible upgrading of a central venous catheters, named “secure lane”.

IV2.2.2 Application for lumbar infusion tests

In another application, the invention can be applied for diagnosis of normal pressure hydrocephalus. This condition is caused by an elevated intracranial pressure (ICP) due to reduced absorption capacity of cerebrospinal fluid. Several diagnostic procedures are currently used to make the diagnosis. One method is the lumbar puncture tap test (figure 2), which assesses the absorption capacity. For this test, saline is infused into the CSF space while the pressure is measured. A steep rise in pressure indicates reduced absorption. A clinician, wanting to diagnose normal pressure hydrocephalus using conventional techniques, will employ two lumbar puncture needles each inserted into the spinal lumbar cavity. One needle is used to inject a liquid medium (e.g. water) into the cavity while the second needle, attached to a pressure gauge, is employed to measure hydrostatic pressure in the cavity which corresponds to the intracranial pressure (ICP). Alternatively, measurement of the ICP may be performed using a single large diameter needle for both infusion and measurement. The use of two needles or a larger needle leads

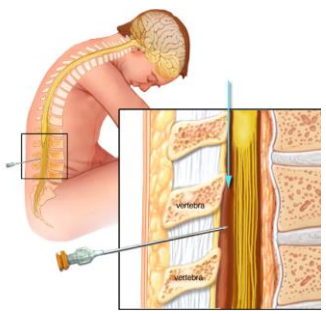

Figure 2: Lumbar infusion test (© Mayo foundation)

to patient discomfort and an increased risk of side-effects. It is important that the ICP is measured reliably to allow the correct determination of the ICP as a function of the infusion rate, since this ratio has an important diagnostic value.

Application of the invention permits minimal invasive performance of a lumbar infusion test: By employing the capillary tube assembly inserted into the needle used to inject liquid medium, a more accurate estimate of ICP is obtained, while the procedure requires the use only of a single lumbar puncture needle. The capillary tube assembly provides an economical solution to the problem of inaccurate pressure measurement, and can be deployed on existing invasive tube assemblies (e.g. multilumen catheter, lumbar puncture needle) without significant adaptation.

IV2.3 Further reading

See appendix 3 for a more detailed description of the patent.

3

IV3 Secure Lane

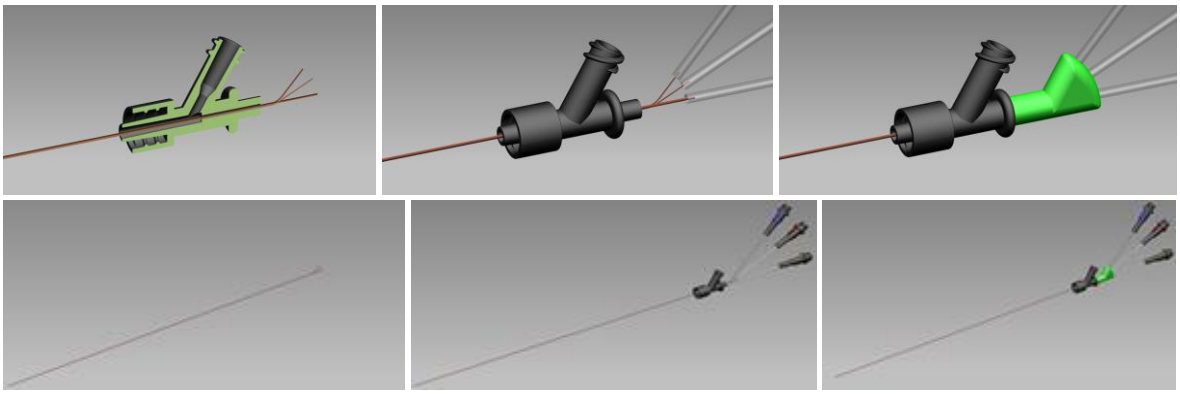

Figure 1: architecture of the Secure Lane. A (brown) triple-lumen capillary is advanced in a (black) injection-molded adaptor, and 3 (grey) extruded tubings are positioned over the separate capillary lumens. The (green) polymer piece is overmolded to secure the assembly.

IV3.1 Design of the device

A convenient device must be easily and safely attached to an in-situ central venous catheter, subsequently it must fluently slide into the in-situ catheter without kinking of the capillaries, and safely/reversibly attached. This must all be done in a sterile matter, with minimal complexity, teaching requirements or sterility precautions.

IV3.2 Choice of materials

Initially poly-imide was deemed most suitable because of its high stiffness (allowing for a very thin wall-thickness. Several polymers were evaluated on their mechanical characteristics.

Eventually, Pellethane®, an aromaticTPU was evaluated as most suitable. Particular convenient is its property of high stiffness at room temperature, a favourable attribute during insertion, which decreases significantly at 37°C, and is therefore less traumatic in situ. Because of these properties, this material is already used for other types of catheters and are already available as multi-lumen tubes. In addition, its biocompatibility has been established, this material also has a favourable wall thickness, and does not need an extra coating.

We performed flow studies, where a syringe pump was used to have a precisely predetermined flow. The pressure needed to maintain a steady flow over a 30cm capillaries length was measured using conventional pressure sensors.

These studies are performed to evaluate if the needed inflow pressure to attain clinically required flows are within the range of conventional syringe pumps.

IV3.3 In-vitro fluid dynamics tests

- In a first evaluation, several capillaries were evaluated to determine the pressure gradient as a function of the flow in capillaries of 30cm length with different diameters. Secondly, based on these findings and other biocompatibility properties - such as kink-resistance , thrombogenicity and elasticity – several types were chosen to integrate in the prototype.

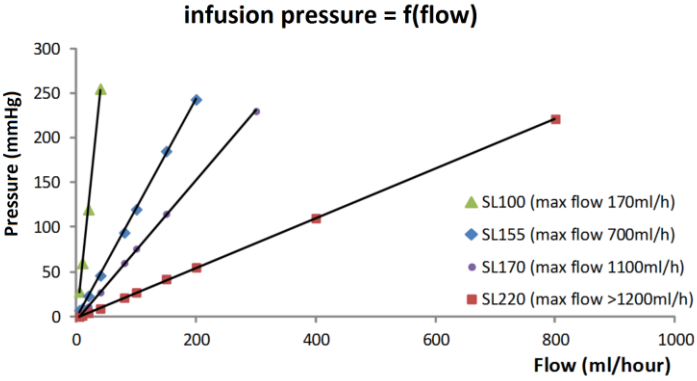

Figure 2: Infusion test using syringe pumps to evaluate the infusion pressure as a function of the flow through sample capillary tubes.

- Several prototypes were assembled with different types of capillaries for performing flow measurements of the capillaries in combination with single-lumen central-venous catheters. A favourable combination seems to be an upgrade from a single-lumen to a triple-lumen catheter making use of a capillary of 22G and a 23G (=2.6 Fr outer diameter), combined with a single lumen 16G catheter. Under a 1 meter water pressure, the free-flow rate over the main channel was decreased to 1360 ml/hour, which is comparable with the free-flow rate of the largest lumen in a conventional triple-lumen catheter. With conventional syringe pumps, fluid can be administered over the capillaries with respective flow rates of 300ml/h and 180 ml/h respectively.

- The quality of the pressure waveform transduction through the capillaries was evaluated in a dynamic simulation tests. A computer operated electromechanical simulator was build where recordings of central venous pressure curves could be regenerated in a pressure tank. In this test simulation, the impedance of the capillaries was quantified and compared with the gold standard : measurement through a 18G single lumen catheter. All these data were recorded using a Datex® monitor and exported to PC for analysis.

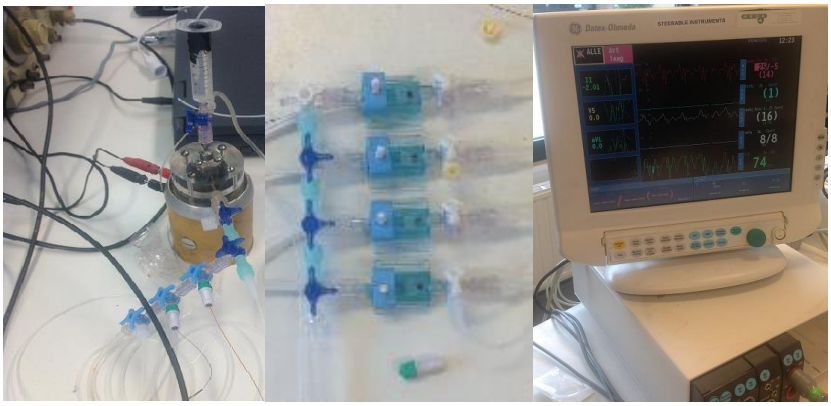

Figure 3: electromechanical simulator, pressure gauges for parallel registration of generated pressure waves, visualisation of pressure waves for data export and quantitative analysis.

- A pulsed flow simulator was built for visualisation of pulsatile fluid flows – simulating flow in the caval vein - around a classical multilumen catheter and around the combination of an upgraded single lumen catheter. Red and blue ink was infused through different small lumina to visualise the degree of mixing in different combinations and configurations.

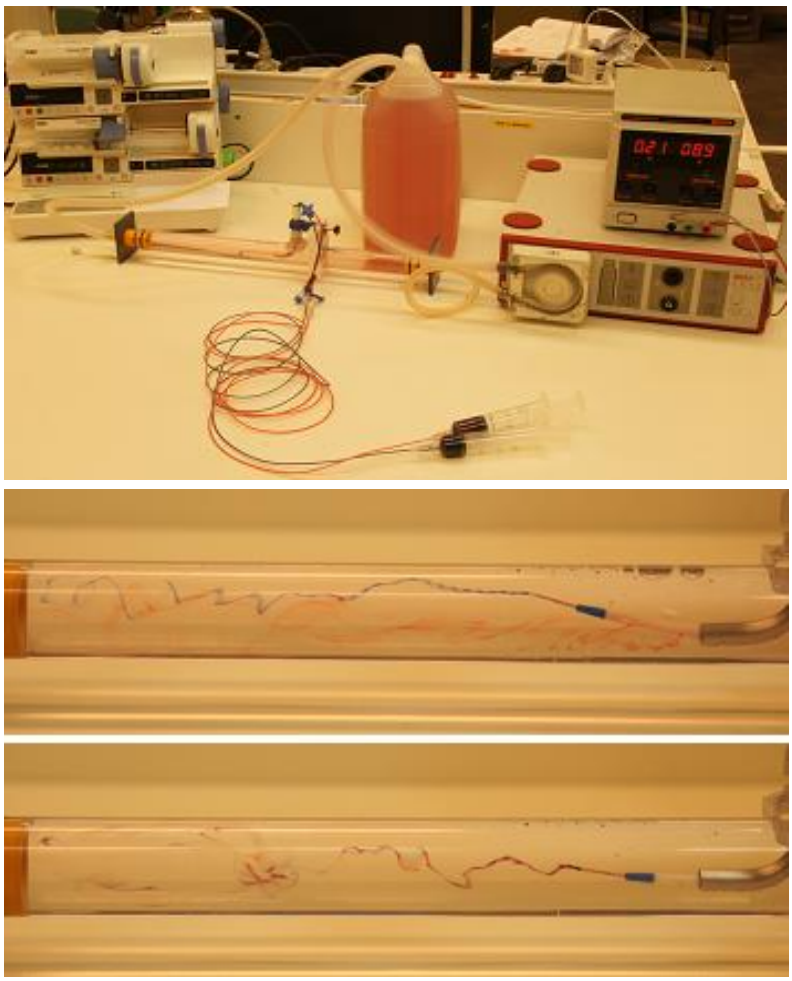

Figure 4: Pulsed flow simulator to visualise the mixing of fluids in pulsatile medium, in different configurations.

IV3.4 In-vivo testing

Theoretically perfect pressure gauges need no volume displacement in order to transmit the distal pressure to the electronic transducer. Standard disposable pressure transducers used in clinical practice however do have a minute but significant internal volume displacement. This causes an impedance to pressure oscillations which becomes more significant in small-lumen catheters. In order to determine the degree of impedance (visualised as flattening of the oscillations), recordings were made of the central-venous pressure waveform through the main (large-bore) lumen of the central venous catheter, as well as through the secure lane. This indicates that in the smallest lumina, the particular oscillations are flattened, but the mean central venous pressure remains accurate. These results were equivalent with the in-vitro measurements.

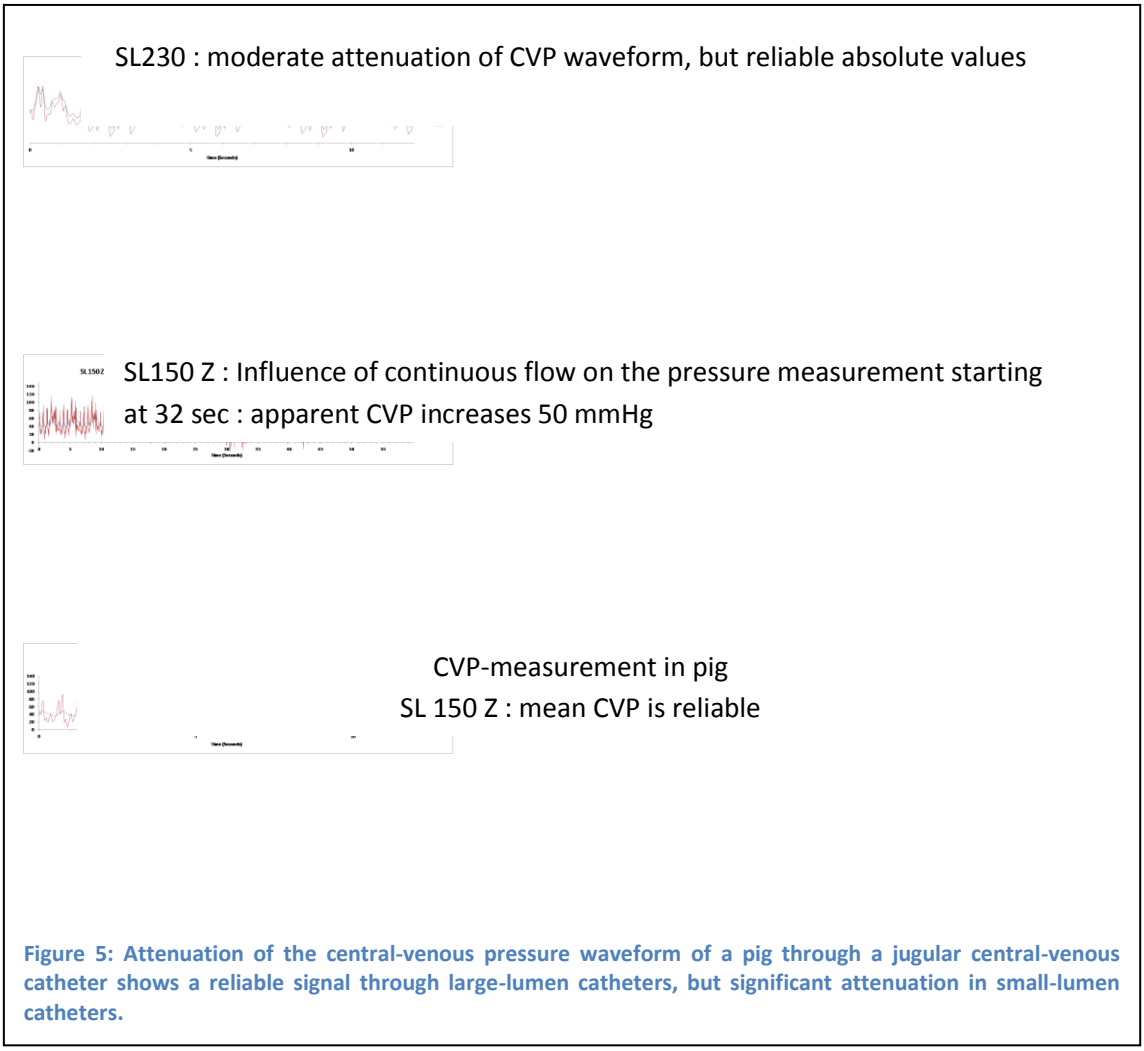

Figure 5: Attenuation of the central-venous pressure waveform of a pig through a jugular central-venous catheter shows a reliable signal through large-lumen catheters, but significant attenuation in small-lumen catheters.

IV3.5 The applicator packaging

The applicator package comprises the capillary tube assembly and a protective cover allows the capillary tube assembly to slide longitudinally within a void of the cover. The protective cover maintains the capillary tube assembly in a sterile environment until it is completely introduced in the main catheter. A stainless steel guidewire is located in the largest capillary channel to optimise stiffness during introduction. The guidewire is removed after correct placement of the secure lane.

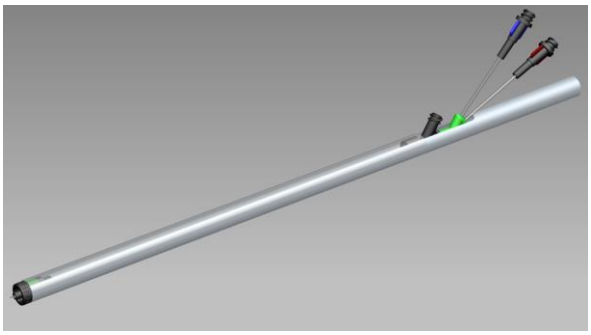

Figure 6: capillary tube in its applicator packaging

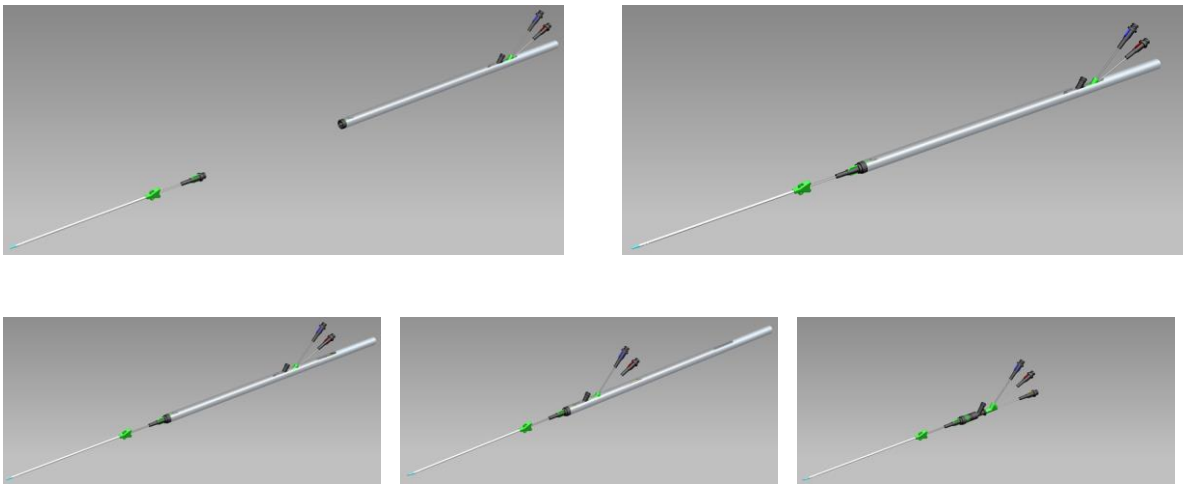

Figure 7: capillary tube in its applicator packaging: The luerlock of the intermediate part is screwed to the main catheter, the secure lane is advanced into the catheter, and after the adaptor is tightened to the intermediate part, the applicator is removed.

IV3.6 Advantages of our solution

Because swapping of the catheter is no longer needed, this will obviate all the complications of swapping in most cases. In addition however, because upgrading to a larger number of lumina becomes extremely easy and atraumatic, there will be much less restrictions to start with the minimal number of lumina necessary – and therefore even more decrease many risk factors attributable to higher-lumen catheters – because in case of changing circumstances an upgrade/downgrade is readily available.

Many medical and financial advantages exist in favour of the upgrading system:

- Catheter exchanges can be eliminated, reducing the number of catheters that are consumed by one patient.
- Historically, there is often a multilumen used in case it would become necessary (which is often not the case). With the new device available, a single lumen catheter can be used routinely, because the practitioner knows that he can upgrade easily whenever necessary. Therefore, the fact that upgrade is available reduces costs and risks because conventional multilumen catheters can be omitted routinely.
- Less chance of infections because there are less catheter exchanges and because there are no unused connections.
- Old or potentially contaminated SL's can easily be replaced by a new one, also reducing the risk of infection. Because of the burdensome procedure of replacing a conventional catheter, the threshold to do so is conventionally much higher.

V

Conclusion and challenges for further development

1

V1 Conclusion & challenges

From the results of these studies, it can be concluded that continuous pressure measurements, in combination with advanced waveform analysis provides valuable new information for clinical decision-making. While a pressure measurement is a relatively mature technology, newly developed architecture for minimal invasive measurements, as well as innovative combinations of physiological insights, mathematical modelling and the application of modern production technology and computing abilities can still result in significant additional diagnostic advances to improve patient care.

The transition from proof-of-concept devices to medical-grade commercial products involves many factors that complicate this next step. Medical devices that comply with all the necessary requirements for clinical practice must conform with several requirements that limit the choice of the used technologies: biocompatibility concerns and the desire for minimal invasiveness constrains the choice of materials and device dimensions; moreover, because of infections risks, any invasive device should be single-use, which consequently imposes certain economical restrictions. Equipment dedicated for emergency medicine needs to be robust and reliable in a wide range of circumstances, and must be applicable in out-of-hospital environments.

Three medical applications were developed. For each of those, further developments must be realised however before sufficiently reliable prototypes can be produced for clinical application that comply with all the raised restrictions.

V1.1 Oesophageal intubation detection

The first two studies demonstrated the reliability of the hardware and algorithm to provide an immediate diagnosis within high sensitivity and specificity, using a hand-held device, even in patients with decreased pulmonary compliance. The studies also demonstrated that the prototype hand-held device with fully-automatic integrated algorithms gave reliable ventilation detection and tube location. Although these were clinical studies, the measurements were still performed in a hospital setting (operating theatre and intensive care of University Medical Centre Groningen respectively), while the main purpose of the device is in emergency medicine. A next study is being performed at Antwerp University Hospital in emergency out-of-hospital conditions to investigate real-world settings. In addition to an evaluation of the accuracy of the algorithms, this study will also give further information on the mechanical reliability of the device and disposables in those circumstances.

While the device for automatic detection is very promising in its ability to detect the endotracheal tube location starting from reliable pressure signals, several possible causes for inaccurate pressure signals exist however. Some of these are relatively easily manageable while other may be more challenging: electronic failure, or drift on the pressure sensors should be excluded or timely detected with added auto-diagnostic algorithms for system integrity. Mechanical problems with the pressure tubings however are much more challenging, as these are more probable to occur and less straightforward to detect and prevent. The most common problem is clogging of the pressure tubes due to mucus, blood or water which must be anticipated for a device designated for emergency medicine. In particular the distal pressure tubing is at risk of clogging since it is located at the distal end of the endotracheal tube. Clogging of the pressure tubes obviously gives unreliable signals, and risks to give a false or absent diagnosis.

While automatic detection of this problem is in the used prototypes addressed, resolution of the clogging is currently not possible, but is most probably critical before a commercial device can be proposed. In essence, two options can be imagined to direct this problem :

❶ either omitting any pressure tubes, and use direct pressure measurements at the location of interest using tip sensors. This solution has economic constraints at this moment, but technological advances may make those sensors less expensive. While different sensors would be used to obtain the pressure waveform, and the pressure tubings are omitted, the same algorithms as in the demonstrated devices can be used to analyse the pressure signals.

❷ Alternatively, automatic detection of clogged tubes can be implemented, combined with a flushing mechanism to flush the tubes with compressed air. This adds the necessity to add a flushing system to the device, but permits the use of cheap disposables. In addition, different coatings or materials should be evaluated on their tendency to clog with mucus and blood, and on the ease with which the obstruction can be flushed away with air.

An evaluation of the technical challenges and economic considerations of both options must be carried out to determine the optimal strategy for further development.

Finally, the prototype device was designed for clinical testing, but a more robust and ergonomic device will have to be designed before real clinical implementation and pre-commercial testing can be considered. Material choice, ergonomics and aesthetic device design will have to be optimised, as well as compliance with the legal requirements for medical devices.

V1.2 Optimisation and automation of cardiopulmonary resuscitation

In addition to fast and reliable detection of oesophageal intubation, the hardware permits a distinctive analysis of the pressure waveforms to deduct valuable physiological information on the ventilatory and cardiac support during CPR. Because there is a strong interaction between the effect of the positive pressure ventilation and the effect of cardiac compressions, the knowledge of this cardiopulmonary interaction may provide information to maximize the quality of the resuscitation. In a first step, a more ergonomic visualisation of the relevant information may help the resuscitator to optimise CPR.

Iterative algorithms adapting the ventilation and compression settings based on those measurements can potentially optimise resuscitation efforts on an individualised basis for every patients. In essence, the combined proximal and distal pressure measurements allow to accustom the chest-compression depth and ventilation pressures during resuscitation, individually optimised as a function of the physiologic variables of the individual patient. While - because of practical reasons - a target compression depth is currently used as the reference variable, pursuing intrathoracic pressure oscillations within an optimal range may be a more physiological aspiration.

Ergonomically visualised information of the analysis of these pressures may steer the ventilation and compression efforts performed by the human rescuer to optimize the CPR. In a further development, the automatic diagnostics algorithms can be used for direct advice on compression depth, compression frequency, ventilation pressure and ventilation frequency.

Another promising application is the integration of the diagnostic tool with automatic CPR devices and the automatic ventilator. Two separate mechanical interventions are performed to support the cardiopulmonary physiology : sternum compression and pulmonary ventilation. Sternum compressions are thus far predominantly performed manually,

Figure 1: Autopulse® and Lucas® automatic CPR

but automatic devices (fig 1) are increasingly implemented. Pulmonary ventilations are often also performed manually, but automatic ventilation is universally available for many years now. Currently, these two types of cardiopulmonary support are performed largely independent of each other. As a result, the individual differences in cardiopulmonary interaction are almost completely neglected. Particularly since automated chest-compression devices (such as the Autopulse® and Lucas® device; fig. 1) are increasingly used, and will probably be integrated within an "intelligent" monitoring system and ventilator for CPR, a diagnostic system based on an analysis of intrathoracic pressure measurements may be the source of information for a direct feedback-loop to individualise and optimise chest compression- and ventilator variables.

V1.3 Medical grade secure lane

The constructed devices for upgrading a single-lumen to a multilumen central venous catheter were demonstrated to comply with the most important physical requirements : use of biocompatible materials, adequate flow capacity, adequate pressure waveform transduction, ease of introduction, and ease of removal. Before the device can be tested in routine clinical conditions however, dedicated catheters must be produced where the primary catheter and the upgrade system are perfectly adapted for each other. Importantly, the length of the primary catheter and of the capillary tubes of the upgrade system must be perfectly aligned with error margins below 2 mm. This requires very precise production of the devices dedicated for each other. While this is technically perfectly feasible, guaranteeing this requirement in mass production at competitive prices is not obvious.

A second technical prerequisite that still needs to be addressed is the requirement that the connection between the primary catheter and the capillary upgrade must be dedicated for selective coupling : there must be a perfect fit between those two devices, while it must be impossible to connect the capillary upgrade with other types of central venous catheters. As such, the primary catheter must have a universal luer-lock connection which can be readily connected with other luer-lock systems. In contrast, the capillary upgrade must be exclusively connectable with the dedicated primary catheter, but not with other conventional central venous catheters. This is imperative to prevent mistakes that may harm the patients as a result of incompatible dimensions of the capillary system and the primary catheter. Conventionally, in order to maximise convenience, essentially all appliances for intravenous access use the universal luer-lock connection. This guarantees the possibility to securely join any type of appliance with any other. While this is advantageous for most appliances, this must be avoided for the capillary upgrade. Our prototypes were made with conventional universal luer-lock connectors, and therefore lack any selectivity. While designing a selective luer-lock to solve this requirement is readily conceivable, a most optimal design for such a selective connector still needs to be addressed.

Because of the particular market environment of central venous catheters, commercialisation of such a device should most probably be done by a large player in the catheter industry. Both the required exclusive compatibility with the primary central venous catheter, and the legal requirements that must be respected for production of devices that are deployed in the central venous system, imply that production of these device is probably best managed by a company with an existing assortment of central venous catheters.

In a first step towards clinical testing in patients, medical grade devices should be designed and produced. Because the most challenging parts (mainly the multilumen capillaries) are already on the market for use in other applications, this should be very feasible. Once medical grade prototypes are developed, clinical studies should be performed to prove the clinical value, safety, practical advantages and market potential.

A first enquiry revealed that cardiac anesthesiologists, as well as intensive care specialists, are particularly interested to evaluate its value in routine cardiac surgery. In these procedures, a 3-lumen catheter is required during the 3-6-hour surgery, but in most cases, a subsequent reduction to a single lumen catheter would be beneficial for the next few more days. The availability of a convenient upgrade/downgrade system would significantly ease decision making and improve patient safety. An initial assessment in cardiac or abdominal surgery is therefore probably worthwhile to explore for initial clinical evaluation.

V1.4 Transendoscopic pressure measurement assembly

While this application is fundamentally different from the secure lane, the device itself, as well as the production requirements are in many domains very similar. Compared to the secure lane, the introduction of the pressure tube in the neuro-endoscope is much less critical, since it is performed by the surgeon in sterile circumstances, and the capillary is introduced in the rigid tube of the neuro-endoscope – which is much more predictable than an in-situ central venous catheter. A dedicated applicator, such as the one designed for the secure lane, is therefore deemed unnecessary. The capillary tube for the transendoscopic application may be a single lumen capillary (in contrast with the secure lane, where a multilumen capillary is preferred), which also makes the construction of the connection device less demanding. Finally, conventional luer-lock connections may be used since exclusive compatibility with the neuro-endoscope is of no concern. As such, the production and marketing of this application is significantly easier than the secure lane. Conversely however, the global number of neuro-endoscopic procedures with high rinsing rates is very low, compared to the number of used central-venous catheters, and therefore from a commercial perspective less attractive.

Devices for intra-cerebral use must comply with very strict legal production requirements; the production of the first commercial clinical-grade prototypes will therefore have to be made by a dedicated company which complies with all these requirements. In anticipation, studies for

trans-endoscopic intracranial pressure measurement during neuro-endoscopy must be designed to confirm the clinical value, which is essential to progress to commercial production. Prototype studies can be performed using medical grade luer-lock adapter pieces and commercially available PIC-catheters. These could be assembled by the surgeon immediately before the start of the surgical procedure on the sterile field in the operating theatre. While such an assemblage by the surgeon is impractical for routine practice, in a research setting, it can be done to perform the necessary feasibility studies. Because the aim of such is a study is to compare the non-invasive pressure measurements with conventional invasive gold standards, and to quantify rinsing restrictions, a low number of patients should suffice to deliver the required information in clinical circumstances. Secondly, a commercial partner in the field of neuro-endoscopy can be approached to evaluate the market potential for a dedicated device.

Likewise, a neurosurgeon performing a dual needle lumbar infusion test could perform a proof-of-concept evaluation in some patients to evaluate the pressure values described in chapter IV.2.2.2, making use of self-assembled ultrathin PIC catheters and dedicated luer-lock adaptor pieces. Again, this study should demonstrate the potential of a dedicated device, after which it can be considered for commercialisation.

V1.5 Challenges for the near future

As for any invention that ultimately reaches its end-users through commercialisation, proof-of-concept devices may offer promising results in a controlled, academic environment, but this is only the first step before wide distribution and application can be considered.

Any company that would consider marketing a device must first analyse its market potential and financial risks and opportunities to determine the global business viability. A first prerequisite to have any chance for market potential is that the device must ultimately prove a significant end-user value, and preferably should offer a solution for a perceived problem. Secondly, industrial production should be feasible with respect to real market conditions and legal requirements. The device will also have to be produced in such a way that it is reliable in the different circumstances where it will ultimately be applied.

Particularly for medical devices, liability in case of improper use, device failure, or application in unfit circumstances must be anticipated and is an important consideration in the evaluation of the business case.

As such, for each of the developed devices, the step from academic prototyping to pre-commercial devices will demand thorough evaluation and management of those risks. Ultimately, after a positive evaluation of the business potential, a small batch of commercial devices will have to be manufactured, complying with all the technical and legal requirements, and small scale clinical studies will have to be performed to confirm the value and reliability of the devices, before large-scale application may be conceived.

As such, the organisation of those steps, and the coordination of the clinical studies are an challenge and opportunity to prove the real-world benefits of the devices and to ultimately improve future patient care.

VI

Appendices – patent applications

1

VI1 Methods and systems for analysing resuscitation

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United States
Patent Application Publication

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Date of PCT filing: Dec.10. 2009
Inventors: K Monsieurs, **AF Kalmar**

Abstract

This invention relates to a system generating control signals for compressing or ventilating, respectively. The system comprises a computing device dedicated to process, for a resuscitation, information regarding a compression parameter and/or ventilation parameter, as function of a parameter indicative of blood circulation, a process component for evaluating the different values of the chest compression parameter and/or ventilation parameter as function of the parameter indicative of the blood circulation. The obtained function will generate a value for chest compression parameter and/or the ventilation parameter respectively, and a control signal generator for generating control signals according to the derived ventilation parameter or chest compression parameter.

VI1.1 Field of the invention

This invention belongs to the field of medical devices. More particularly, the present invention relates to methods and systems for analysing resuscitation, for example in case of intubation of a patient, or for optimising chest compression depth and ventilation pressure.

VI1.2 Background of the invention

When a patient needs positive pressure ventilation or chest compression (resuscitation), a number of clinical problems may arise. One known clinical problem is the occurrence of increased intrathoracic pressure during resuscitation. There are numerous case reports of restoration of a spontaneous circulation after cessation of resuscitation efforts.[1] This phenomenon, also referred to as the "Lazarus phenomenon" is explained by trapping of air during ventilation and the presence of "positive end expiratory pressure" (PEEP) resulting in inefficacy or failure of the resuscitation. As trapped air escapes and the positive end expiratory pressure disappears after cessation of the resuscitation, this may allow blood to start flowing to the heart again and therefore result in a restoration of circulation even after CPR efforts have been stopped.

VI1.2.1 Hyperventilation and air trapping during CPR

Animal studies have also shown that hyperventilation during resuscitation results in decreased coronary perfusion pressure and in excess mortality.[2] In a small clinical observational study of 13 patients with cardiac arrest, high ventilation rates and increased intrathoracic pressures were recorded.[3] Hyperventilation is common during resuscitation. Such findings have resulted in the international recommendation to avoid hyperventilation during resuscitation for cardiac arrest.

Early detection and avoidance of hyperventilation and subsequent increased intrathoracic pressures during resuscitation may be an accurate means for preventing failure of resuscitation and for increasing survival chances and therefore is an important clinical issue.

VI1.2.2 Oesophageal intubation

Another known problem with resuscitation is wrong intubation. Wrong intubation into the oesophagus, if detected too late, may result in the death of the patient because of a lack of oxygen and ventilation. Wrong oesophageal intubation is a common problem in emergency situations, both during cardiac arrest and in patients with spontaneous circulation (the latter needing protection of the airway such as in neurotrauma or in cases of respiratory failure).

A variety of methods to detect correct, i.e. tracheal, intubation are known such as for example clinical assessment by looking at chest movements, by auscultation of the chest and of the epigastrium, by assessment of the suction of air through the tube by means of a self-inflating

bulb or syringe, by capnography and capnometry, by chest impedance measurements through surface electrodes, etc. None of these techniques are both highly sensitive and specific.

VI1.2.3 Assessment of the quality of CPR

Current state of the art methods to assess quality of resuscitation mainly use impedance measurement of the chest wall and accelerometers placed on the breastbone. The quality of ventilation is often currently addressed by impedance measurements between two electrodes attached to the chest of the victim. This provides reasonable accurate measurements of ventilation frequency and very rough measurements of volume. The quality of chest compression is determined by accelerometers placed on the breastbone of the victim. These provide reasonable accurate measurements of compression frequency and dept.

All these technical solutions to improve the quality and safety of intubation, ventilation and chest compression are in their early stages of clinical application and there is room for improvement.

VI1.3 Summary of the invention

4. An accurate analysis of resuscitation
5. An accurate detection of the proper position of an endotracheal tube, substantially independent of the person who needs to perform the detection
6. An accurate and quick detection of spontaneous cardiac activity

It is an advantage of embodiments according to the present invention that :

- the system and method can be developed into a standalone device or that it can be incorporated into existing resuscitation monitors and ventilators.
- for some existing monitors, defibrillators or ventilators, the method can be implemented by introducing software without requiring complex additional hardware components and without the need for additional adjuncts such as bulbs, syringes or capnometry equipment. It is for example sufficient that a spare pressure channel is available or can be provided on the monitor, defibrillator or ventilator for allowing receipt of a pressure signal in combination with the use of a pressure sensor.
- a system is obtained allowing quick and automated detection of appropriate resuscitation using an endotracheal tube.
- using such algorithms for evaluating sequential pressure values, the improved accuracy may also permit more accurate resuscitation.
- spontaneous cardiac activity can be detected rapidly.

A pressure waveform analysis may be performed to determine the location of the endotracheal tube using the following steps:

- a tracheal dP/dt value higher than a first predetermined value,
- followed by a tracheal dP/dt value with an absolute value lower than a second predetermined value,
- followed by a high negative tracheal dP/dt value having an absolute value higher than a third predetermined value.

Using these principles, an accurate detection of the location of an endotracheal tube can be obtained. The obtained pressure waveforms furthermore may be used for determining a true compression.

The system may be adapted for receiving pressure values sensed within an endotracheal intubation tube. The endotracheal intubation tube may comprise a pressure sensor catheter having a catheter tube filled with air. It thereby is an advantage that small pressure differences induced by compression or spontaneous heart activity can be detected. The endotracheal pressure thereby may be used as surrogate for intrathoracic pressure.

VI1.4 Brief description of the diagnostic algorithm

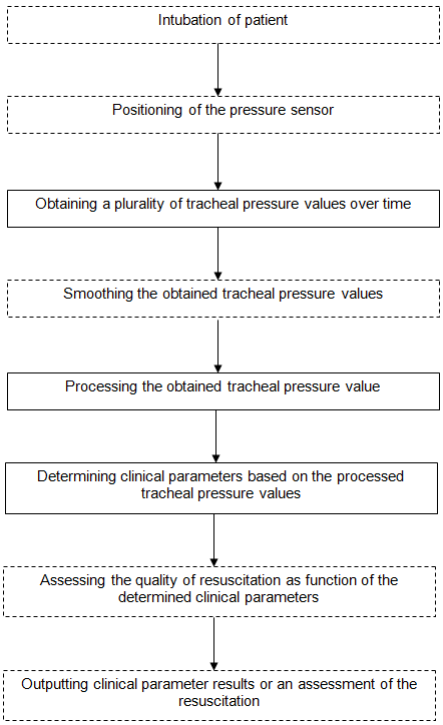

Figure 1: a schematic representation of a flow chart of the algorithm that may be used for deriving information for the analysis of resuscitation according to an embodiment of the present invention.

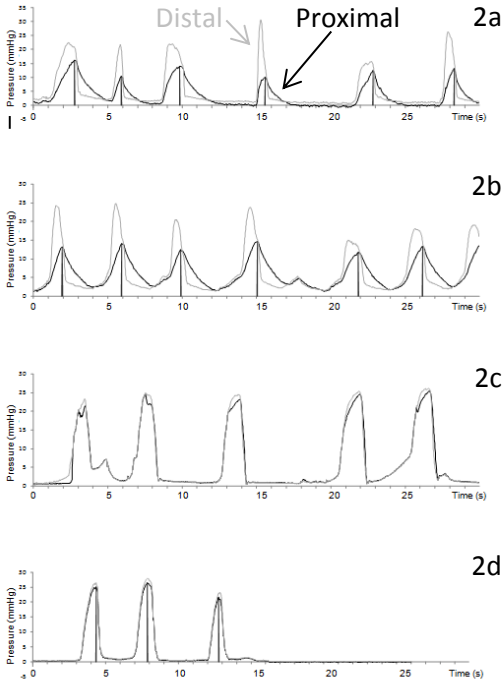

Figure 2a, 2b, 2c and 2d: pressure curves for a distal measurement point and a proximal measurement point in case of tracheal intubation (2a and 2b) and in case of oesophageal intubation (2c and 2d) as can be obtained according to embodiments of the present invention.

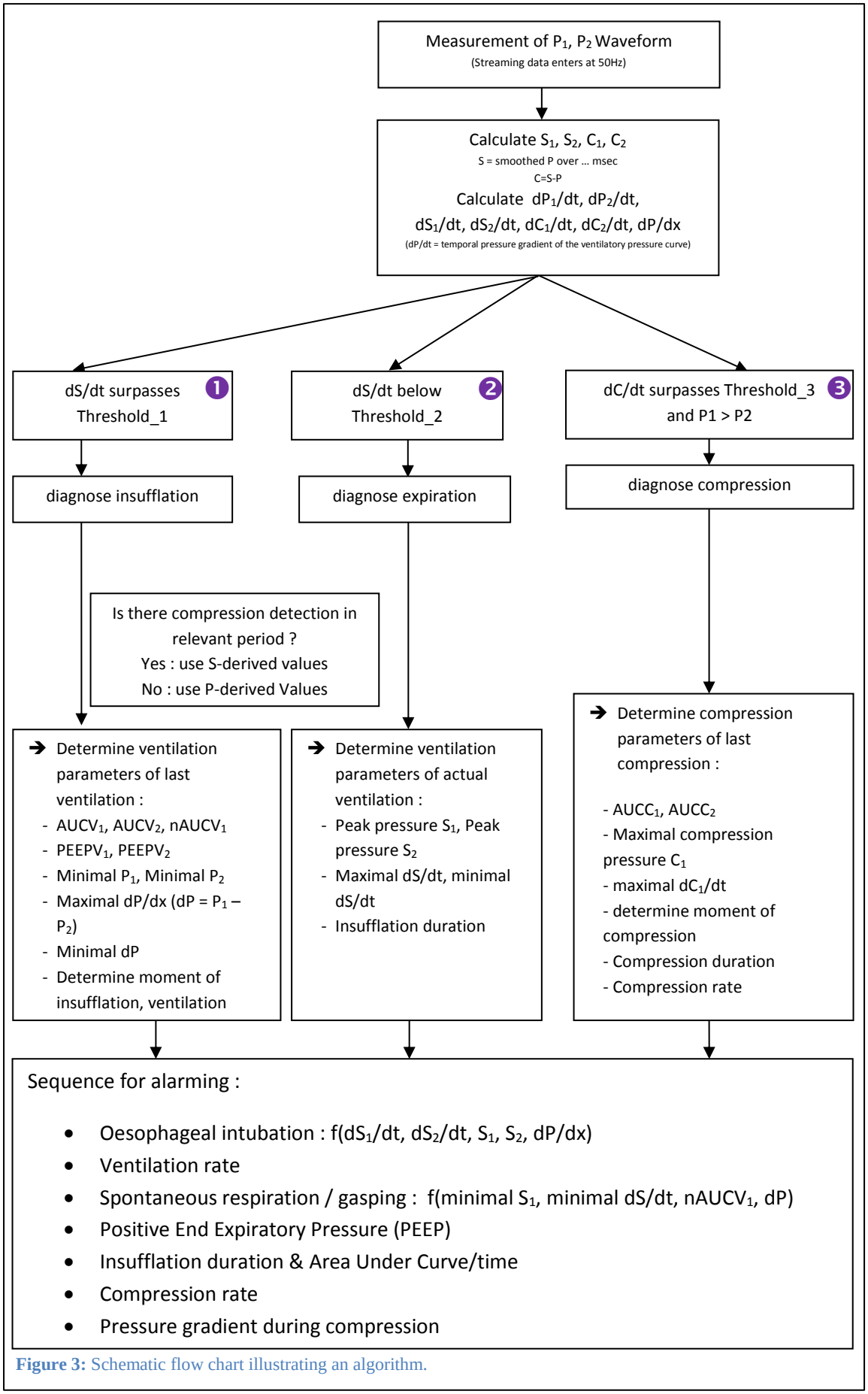

Figure 3: Schematic flow chart illustrating an algorithm.

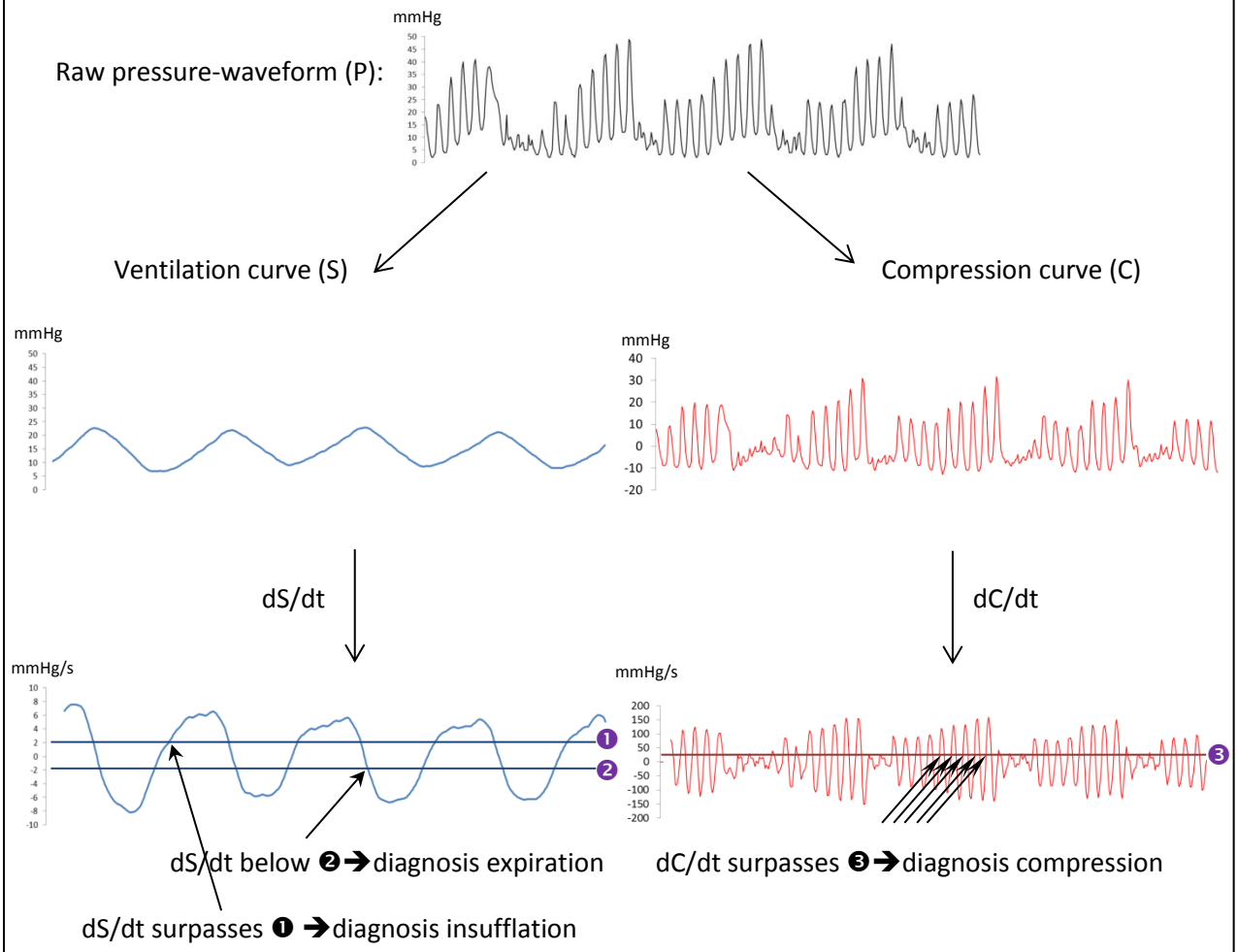

Figure 4: Example of an automatic analysis of the raw pressure recording P_x to extract information on ventilation and compression. This illustrative figure was not part of the patent application. The curve P is a recording at 150Hz of a patient being mechanically ventilated while performing chest compressions. The curve results from a superposition of the effects of ventilation and chest compressions. An averaging algorithm calculates S_x from the pressure curve P_x. The S_x-curve reflects the intrathoracic pressure curve resulting from ventilation as if no chest compressions were performed. Subsequently, the S_x-curve is subtracted from the P_x-curve to calculate the C_x-curve. The C_x-curve reflects the intrathoracic pressure curve resulting from chest compressions as if no ventilation was performed. The C_x-curve looks very similar to the P_x-curve, but the Y-axis demonstrates that the values oscillate around 0 mmHg. The apparent continued presence of ventilatory oscillations are a result of the cyclic negative pressures in the P_x-curve resulting from stronger recoil with subsequent more pronounced negative pressures. In order to operationalize specific events, the first derivative of both the S_1-curve and the C_1-curve is calculated. When the first derivative crosses a certain threshold, a specific event is diagnosed:

- A sharp increase in the S_1-curve (resulting in a high dS/dt value) is a result of insufflation of air.
  → when dS/dt increases above a threshold value ❶, insufflation is diagnosed.

- A sharp decrease in the S_1-curve (resulting in a deep negative dS/dt value) is a result of expiration of air.
  → when dS/dt drops below threshold value ❷, expiration is diagnosed.

- A sharp increase in the C_1-curve (resulting in a high dC/dt value) is a result of chest compression.
  → when dC/dt increases above threshold value ❸, chest compression is diagnosed.

VI1.4.1 Smoothing of the tracheal pressure signal

Smoothing may be performed to compensate for high frequency artefacts, by determining the mean pressure over a moving time-window (of up to 3000 milliseconds) of the measured pressure values. In one example, the time-window over which such averaging may be performed may be 3000 milliseconds (=150 samples). The latter may for example be obtained according to following algorithm, i.e.

From a number of n samples preceding P_x

$$P_1, P_2, ... P_n$$

the corresponding smoothed tracheal pressure value S_x can be determined as:

$$S_x = \frac{\sum_{i=-n+1}^{0} P_{(x+i)}}{n}$$

wherein n is the number of samples in the moving time-window.

VI1.4.2 Calculation of a tracheal pressure gradient

The tracheal pressure value processing component may be used to calculate the tracheal pressure gradient. The gradient thereby may be a temporal or spatial gradient.

- The temporal gradient, which may be expressed as dP/dt, expresses a variation of the pressure over time
- The spatial gradient, which may be expressed as ΔP, expresses a variation of the pressure between two different locations.

In one example, the time window over which determination of the gradient may be performed may be 150 milliseconds. For samples P_x or the smoothed sample S_x the gradient value G_x may be determined as

$$G_x = \left(P_x - P_{(x-n)}\right) * \frac{R}{n}$$

respectively

$$G_x = \left(S_x - S_{(x-n)}\right) * \frac{R}{n}$$

where :

- R is the sampling rate. (expressed in #samples/s)
- n is the number of samples in the time window.
- P_x is the pressure value (expressed in mmHg) at sample point x.
- S_x is the pressure value (expressed in mmHg) of the smoothed curve at sample point x.
- G_x is the gradient in pressure (expressed in mmHg/s) between sample point (x-n) and sample point x. It can be conceived as approximating the tangent to the pressure curve at time point x.

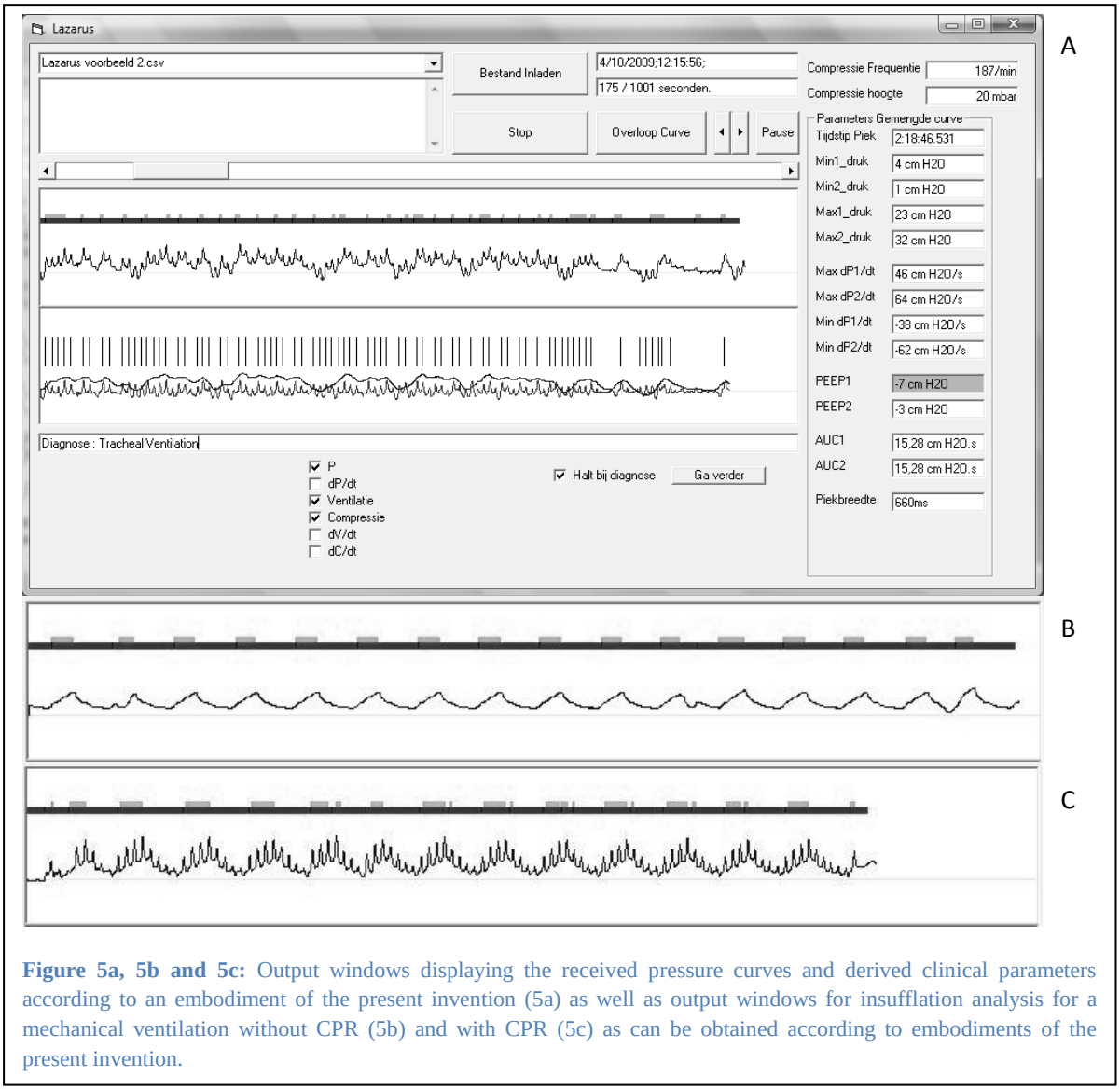

Figure 5a, 5b and 5c: Output windows displaying the received pressure curves and derived clinical parameters according to an embodiment of the present invention (5a) as well as output windows for insufflation analysis for a mechanical ventilation without CPR (5b) and with CPR (5c) as can be obtained according to embodiments of the present invention.

VI1.5 Oesophageal intubation detection

In a first example, the system, more particularly the clinical parameter determination component, may be adapted for determining detection of the location of an intubating tube, i.e. oesophageal or intratracheal intubation, based on at least one pressure gradient value. When oesophageal intubation is performed, it has been found that the pressure profile typically consists of a fast increase of the sampled pressure or smoothed sampled pressure, thereafter switching to a plateau pressure, followed by a fast decrease of the sampled pressure or smoothed sampled pressure. It furthermore has been found that in oesophageal ventilation, the maximal ventilatory pressure is never above a relatively low cut-off value even if forceful ventilation is applied by the rescuer. Since the volume of air that can be insufflated into the

oesophagus is much lower, the flow through the tube is relatively low at any pressure during expiration. Consequently, the pressure gradient between the proximal and distal measuring point is lower than for tracheal ventilation.

On the other hand when tracheal intubation, as typically is required, is performed, insufflation of air through the endotracheal tube induces a flow of air into the lungs. Because of the capacity of the lungs to accept a significant volume of air, the flow of air through the tube (e.g. expressed in ml/s) results in a clear pressure gradient between the proximal and the distal measurement point, if two points are used for measuring tracheal pressure or receiving info thereof. Furthermore at expiration, since an important volume of air can be exhaled when the insufflation pressure is released and the patient is allowed to exhale, the pressure at the proximal measuring point drops immediately, while the pressure at the distal measuring point only drops slowly due to the important volume of air that needs to flow through the tube. Again a pressure gradient develops between the two measuring points. Because of the lower compliance of the oesophagus compared to the lungs, during insufflation, the increase in pressure at the distal measuring point is significantly less steep in tracheal than in oesophageal ventilation. The gradient G_t of the pressure signal at time t during insufflation thus may be significantly lower (=the pressure increases less steeply) during tracheal insufflation than during oesophageal intubation. In contrast, during the plateau phase in in the oesophageal intubation, the pressure remains mainly flat ($\rightarrow$ during the plateau phase, G_t is lower in oesophageal than in tracheal intubation). Also at expiration, the pressure drops less steeply in tracheal intubation than in oesophageal intubation : the absolute amplitude of the gradient G_t of the pressure signal is much lower in tracheal than in oesophageal intubation. It also has been found that the maximal ventilatory pressure in tracheal ventilation is much higher than in oesophageal ventilation, even though the gradient G_t of the pressure is significantly lower. The difference in compliance between the lungs and the oesophagus thus results in very significant differences in the characteristics of :

1. the pressure gradient over time of the endotracheal pressures (dP/dt)
2. the pressure gradient between two different measuring points at a given time (ΔP).

It has been found that using the pressure curves obtained during the initial ventilation cycles, e.g. during the first four ventilation cycles, correctness of the intubation can be determined, i.e. distinction can be made between tracheal intubation or oesophageal intubation. It is an advantage of embodiments of the present invention that sampling the pressure signal generated by the ventilations can be performed as soon as intubation has been performed. This allows to quickly distinguish between oesophageal and tracheal intubation. The latter can be indicated, e.g. using an alarm or warning signal in any suitable way, e.g. using a green light when tracheal intubation is obtained and using a red light when oesophageal intubation is obtained. According to embodiments of the present invention, the system thus may provide confirmation of the localization of the tube being intratracheal or oesophageal upon intubation. This information will allow the health care provider to establish correct intubation or to remove and replace the tube.

VI1.6 Assessment of chest compression and compression rate

In another application, the gradient dP/dt may be used for determining the onset and release of chest compressions. When the dP/dt is above a predetermined cut-off value, a true compression may be suspected. If dP/dt with a negative value of at least a predetermined value is subsequently detected within 500 ms and the highest pressure value between both dP/dt values is above a predetermined value, a true compression may be confirmed. The highest pressure value may be referred to as peak pressure. The system may be adapted to use the time between the two or some of the last maximal pressure values for determining a rate of chest compression. The system may be adapted for providing a notification when the determined chest compression rate is too high or too low. The lowest pressure value Px in the 250 ms after the lowest dP/dt value is the minimal pressure. Ideally, to achieve optimal venous return and blood flow to the heart, this value should be zero or negative. The system may be adapted for providing a warning or alarm notification if the minimal pressure does not return to baseline. Evaluation may be performed during several subsequent compressions. The latter may for example occur when there is incomplete release of compression, or in case of inappropriate ventilation mode. The system also may be adapted for determining a mean pressure generated by a chest compression. The latter may be determined by

$$P_m = \frac{\sum_{i=T_1}^{T_2} P_{(i)}}{T_2 - T_1 + 1}$$

with point T_1 and T_2 being the time point of maximal dP/dt values of the two last compressions. The system furthermore may be adapted for determining a difference between the Peak Pressure and the Minimal Pressure, referred to as ΔP. If the amplitude of ΔP is too low, a warning or alarm notification may be provided.

VI1.7 Assessment of return of spontaneous circulation

In another application, the system is adapted for detecting spontaneous circulation. Spontaneous circulation may be evaluated based on a pulse pressure PP determined as follows : With M_1 being the minimal pressure value in a time span of 200ms before the positive dP/dt value is obtained and M_2 being the minimal value in a time span of 200ms after the negative dP/dt value, the minimum pressure can be determined as

$$P_{\min} = \frac{M_1 + M_2}{2}$$

The peak pressure P_{peak} can be determined as the highest pressure value between the positive dP/dt and the negative dP/dt. The pulse pressure PP then is defined as

$$PP = P_{peak} - P_{\min}$$

If the pulse pressure is higher than a minimal predetermined value, spontaneous circulation

may be confirmed. Advantageously, also a dP/dt higher than a minimum value and a positive dP/dt value followed by a negative dP/dt value of minimal absolute value within 200ms are factors pointing to the presence of spontaneous circulation. The combination of the above three aspects (pulse pressure, dP/dt value and subsequent positive and negative dP/dt) may allow confirmation of spontaneous circulation with higher sensitivity/specificity.

VI1.8 Assessment of the origin of pressure changes

The tracheal pressure gradient may be a spatial tracheal pressure gradient based on tracheal pressure values determined at different positions in the endotracheal tube. The behaviour of the tracheal pressure values at the different positions may allow to derive the origin of pressure built up. If for example an abrupt pressure pulse is measured at the distal end of the endotracheal tube and a smaller pressure pulse is measured at the proximal end of the endotracheal tube, the tracheal pressure signal is more likely representative of a chest compression. If for example a weaker pressure pulse is measured at the distal end than the pressure pulse measured at the proximal end of the endotracheal tube, the tracheal pressure signal is more likely representative of a ventilation.

VI1.9 Assessment of ventilation variables

The method and/or system may be adapted also for determining further clinical parameters. The system therefore may comprise an additional parameter determination component. The system and/or method may for example be adapted for determining the mean pressure M_x at sample point x by averaging the sampled pressure values or the smoothed values thereof over a large time window, e.g. over a time window of 5000ms. In further embodiments, this value may be used for determining whether the sampled pressure value (P_x) or the smoothed sampled pressure value (S_x) is below or above the mean pressure (M_x) and the inversion point, for determining the highest value H of the sampled pressure values or the smoothed sample pressure values and/or for determining the lowest value L of the sampled pressure values or the smoothed sampled pressure values. Both timing and value of the maximal and minimal ventilatory pressure can be derived. Evaluation of the sign of ((P_x or S_x) - M_x) may allow to determine whether the sampled or smoothed sampled pressure is below or above mean pressure. Determination when ((P_x or S_x) - M_x) equals zero may allow to determine inversion points. Calculation of the mean pressure may be performed continuously, using a moving window.

The system optionally may be adapted for diagnosing a **ventilation cycle**, with a true sign inversion, if the highest sampled, optionally smoothed, pressure value minus the lowest sampled, optionally smoothed, pressure value is larger than a predetermined value, e.g. larger than 5cmH_2O.

The system optionally may be adapted for determining the **ventilation frequency**

based on the time between two sub-sequent peak ventilatory pressures. In another embodiment, the system may be adapted for determining within every ventilation cycle, the fraction of the time during which the **ventilatory pressure** is higher than a certain value. The obtained fraction may be used as signalling function, e.g. when the fraction is higher than a reference value an alarm signal may be provided. In yet another embodiment, the system may be adapted for determining whether a minimal ventilatory pressure is higher than a reference value. The latter may be used as signalling function, e.g. when the minimal ventilatory pressure is higher than a certain value, an alarm signal may be provided. This would signify the **presence of PEEP** (Positive End-Expiratory Pressure) and a risk of decreased venous return and lower efficacy of the chest compressions. The system may be adapted for providing an alarm signal if the ventilation frequency is or is repeatedly higher or lower than a certain value. The system may be adapted to provide an alarm signal if the maximal ventilatory pressure is higher than a certain value. In one embodiment, the system may be adapted for providing a notification of **spontaneous respiration** if a negative ventilatory pressure below a certain value is detected.

In a further step, the method and/or system may be adapted for assessing the quality of the resuscitation based on the measured clinical parameters. Such an assessment may be performed in an automated and/or automatic way and results may be outputted or it may be performed by the user based on outputted determined clinical parameter results.

The method and/or system therefore advantageously also may be adapted for optionally generating an output representative of the assessment of at least one clinical parameter or a related, e.g. physical, condition or an assessment of the resuscitation

VI1.10 Integration of pressure values with other parameters

In order to further improve the information obtained with the system, information from endotracheal pressure analysis can be integrated with other parameters to improve the sensitivity/specificity of automatic diagnostic algorithms. For example, appearance of a peak in the intrathoracic pressure systematically following the R-wave on an ECG indicates a higher probability of the presence of a true spontaneous cardiac compression than conclusions drawn when the ECG-information is absent.

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2

VI2 Endoscopic pressure detection assembly

Europäisches Patentamt
European Patent Office
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EP 2 598 015 B1

EUROPEAN PATENT SPECIFICATION

Adapted from : "Endoscopic Pressure Assembly"

Date of publication and mention of the grant of the patent: 03.09.2014
Inventors : F Dewaele, AF Kalmar, B Blanckaert, C Mabilde

Bulletin 2014/36
Application number: 11748318.0
Date of filing: 26.07.2011
International publication number: WO 2012/013660 (02.02.2012 Gazette 2012/05)

VI2.1 Field of the invention

The present invention relates to a pressure detection assembly for determining pressure in a tissue cavity inspected by an endoscope, and an endoscope adapted with the assembly, and a method for adapting an endoscope.

VI2.2 Background of the invention

Endoscopy is employed in many surgical procedures such as transurethral resection of the prostate/bladder, hysteroscopic procedures such as endometrial resection, fibroid resection, polyp resection, septoplasty, adhesiolysis and arthroscopic procedures. Increasingly, it is being deployed for neurosurgical procedures, to the extent that endoscopic intraventricular procedures are common in most neurosurgical departments. In such procedures, a continuous flow endoscope is frequently used.

VI2.2.1 Continuous flow endoscope

Briefly, a continuous flow endoscope is adapted to allow rinse fluid simultaneously to enter and escape from a tissue cavity *via* separate entry and exit points, as a result of which positive fluid pressure is created inside the tissue cavity which distends the cavity.
A typical continuous flow irrigation endoscope comprises one or more fluidicly isolated lumina present inside an outer shaft. The outer shaft is typically a hollow cylindrical tube which has a distal end which enters a tissue cavity and a proximal end connected to a hub on which an inflow or outflow port is attached for the purpose of instilling or evacuating fluid from the cavity. The irrigation fluid is instilled *via* an inlet port. The instilled fluid travels through a rinse inlet lumen and enters the tissue cavity *via* the distal opening of the rinse inlet lumen. The waste fluid present inside the tissue cavity enters the distal opening of the rinse outlet lumen, and exits the endoscope via the outflow port attached at the proximal end of the rinse outlet lumen.
An optic element (fibre, rigid or chip on tip) is placed inside an inspection lumen of the shaft in order to view the interior of the tissue cavity. An endoscopic instrument may be also placed within another lumen present in the shaft.

VI2.2.1.1 Intracranial pressure during neuro-endoscopy

It was initially assumed that an open outlet channel would prevent a rapid build-up of pressure within the tissue cavity. However, in practice, detached tissue pieces, larger than a critical size, present in the tissue cavity are unable to pass through the rinse outlet port leading to obstruction of the outflow channel which can provide an erroneous pressure reading, and pressure-build up. Additionally, the kinking of outflow tube occurs which can also distort the pressure reading. Raised intracranial pressure (ICP) during neurosurgical procedures is common according to the scientific literature, which can induce intracranial hypertension leading to cardiovascular complications, herniation syndrome, retinal bleeding, Terson's syndrome and excessive fluid resorption.
Direct measurement of pressure in the cavity is the gold standard, however, insertion of a separate catheter through a second burr hole for this purpose is clinically impractical and difficult to justify, particularly for the neurosurgeon.

Consequently, pressure is presently measured at the proximal end of the endoscope at rinsing inlet and outlet as shown in fig 1. which exemplifies measurement of ICP. However, measurements at the proximal ends of the rinse inlet and outlet have been found to correlate poorly with the actual pressure in the tissue cavity. Adding an extra measuring channel would increase the overall diameter of the endoscope reducing its minimally invasive character.

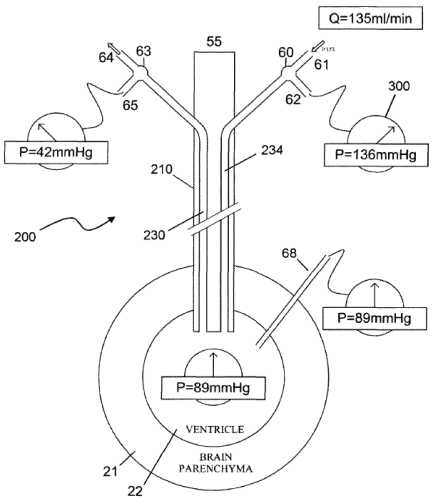

Figure 1: The prior art configuration for measurement of cavity pressure, showing a cross-section through a continuous flow endoscope and measurement of pressure at the proximal inlet and outlet ports.

Fig 1 shows an endoscope inserted into the ventricle within the brain parenchyma, provided with a rinse inlet lumen and a rinse outlet lumen. The proximal end of the rinse inlet lumen is connected to a 3-way valve, one branch connected to a pressure gauge**,** the other branch connected to a pressurized source of irrigation medium. The proximal end of the rinse outlet lumen is connected to a 3-way valve, one branch connected to a pressure gauge, the other branch connected to a waste container. A separate pressure measurement probe is inserted into the ventricle. The true ICP in the ventricle measured by the independent probe is 89 mmHg. A pressure gauge attached to the proximal end of the rinse inlet would indicate a considerably higher pressure (136 mmHg), while a pressure gauge attached to the proximal end of the rinse outlet would indicate a much lower pressure (42 mmHg). From the disparate readings of these proximal gauges, the practitioner must estimate actual ICP, and moreover, be able to determine rapidly blockages to the irrigation circuit.

Pressure measurements at the proximal ends of the inlet and outlet can only provide valid estimations of static ventricular pressures *i.e.* if the rinsing inlet and outlet are closed simultaneously, and pressures are measured after a suitable interval to allow for equilibration of pressures. This is seldom clinically practicable, and it is especially impractical during occasions when high rinsing flows are required such as during brisk bleeding.

VI2.2.1.2 Conventional methods intracranial pressure measurement

Various systems are described in the prior art for the measurement of pressure cavity pressure. For instance US 2009/182201 describes an outer sheath disposed with one or more channels through which a reusable pressure sensor can be inserted, which sheath is fitted over the outer body of an endoscope. The sheath increases the outer diameter of the endoscope, limiting its application in many techniques, including neurosurgery. Moreover, a sterilized sheath is difficult to apply over a sterilized endoscope aseptically. There is thus a need for dynamic pressure assessment that is clinically feasible to implement, which provides a more

accurate measurement of actual pressure in the ventricle, can be applied easily aseptically and avoids the problems associated with blockages.

VI2.3 Summary of the invention

One embodiment of the invention is a pressure detection assembly adapted for use with a continuous flow endoscope provided with a rinse inlet lumen connected to a rinse inlet port said assembly comprising:

4 an elongated member having a proximal and distal end

5 a pressure detecting body at the distal end of the elongated member, configured to provide an indication of ambient pressure

6 a coupling disposed over the elongated member, configured for dismountable attachment to the proximal rinse inlet port of the endoscope,

7 said elongated member configured to conduct the indication of ambient pressure to its proximal end

8 said elongated member further configured for advancement through the rinse inlet lumen, and

9 said fluidic coupling further configured to isolate fluidicly the proximal tip of the elongated member from the rinse inlet port of the endoscope.

VI2.3.1 Detailed description of the invention

The present invention, concerns a pressure detection assembly for use with an endoscope, in particular a continuous flow endoscope, comprising elongated member having a proximal and distal end, disposed at the distal end with a pressure detecting body**.** The elongated member is provided with a coupling proximal to the pressure detecting body configured for dismountable coupling with a proximal rinse port of an endoscope. Throughout the description, a rinse port is mentioned for coupling with a coupling of the elongated member**;** this may be the rinse inlet port or the rinse outlet port**,** but is preferably the rinse inlet port**.** The coupling provides a water impermeable seal. The elongated tubular member is further configured for advancement into the rinse lumen of an endoscope towards the distal tip.

Throughout the description, a rinse lumen is mentioned through which the elongated member is advanced; this may be the rinse inlet lumen or the rinse outlet lumen, but is preferably the rinse inlet lumen. The outer diameter of the elongated tubular member is adapted to permit passage of rinse medium through the rinse lumen when the assembly mounted *in situ i.e.* without substantial hindrance to the flow.

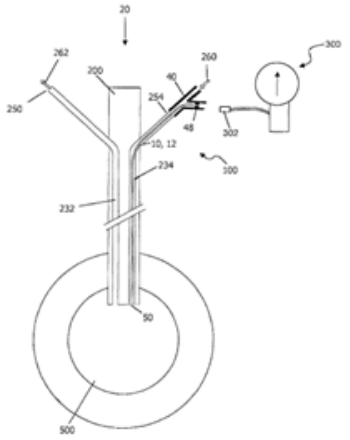

Figure 2: A longitudinal cross-sectional view of a pressure detection assembly of the invention in situ in a continuous flow endoscope.

According to one embodiment of the invention, the elongated member comprises a narrow flexible catheter provided with a catheter lumen for conductance of fluid. The pressure detecting body of the catheter comprises an open port at the distal end of the lumen**.** In normal use, the lumen is filled with a non-compressible fluid for example, a liquid such as aqueous saline solution. Hydrostatic pressure in the vicinity of the pressure detecting body is conducted along the lumen by the non-compressible fluid to the open proximal end of the catheter where a pressure gauge in fluidic connection with the lumen measures the pressure transmitted from the distal end of the catheter. Absolute (or gauge) pressure in the vicinity of the pressure detecting body can thus be recorded.

Advantageously, the assembly provides a measurement of ambient pressure at the distal end of the endoscope that accurately reflects the static pressure in the cavity of the intervention. By contrast, measurement at the rinsing inlet gives a severe overestimation of the true cavity pressure, and if clinicians were to respond to these pressures, this would unnecessarily impede the rinsing efforts of the surgeon. Measurement at the rinsing outlet gives a systematic severe underestimation of the true cavity pressure, which would delay crucial intervention. Pressure could be measured in a static mode, however, this would require pausing the flow of rinsing fluid. Since rinsing is essential to give the surgeon an unobscured view of the cavity, regular pausing impedes progress and increases operating times, so increasing the costs of interventions and the risk of infections. By employing a pressure detection assembly of the invention, which can be applied to an existing endoscope, the pressure measurement, which accurately reflects pressure in the cavity, can be measured accurately and reliably while the endoscope is rinsing.

VI2.3.1.1 Controlling intracranial pressure at a predefined level

Moreover, pressure in the cavity can be exquisitely controlled *i.e*. set to a pre-defined level and maintained at that level. This can be achieved using a closed-loop (feedback loop) system comprising one or more pumps and/or valves and a controller, which controller regulates said pumps and/or valves responsive to pressure measured using the pressure detection assembly of the invention, to maintain pressure at the predefined level. The closed loop system may be advantageously employed to deliberately increase pressure at the intervention site, which pressure increase expedites clot formation in the case of a haemorrhage. Controllably increasing pressure at the intervention site, particularly in the brain, is presently considered a risk to the extent that many surgeons will avoid it. Since the pressure detection assembly of the invention provides such an accurate reading, procedures otherwise excluded as entailing too much risk, now become available through the present invention.

VI2.3.1.1 Sterilisation of the system

The catheter can be made a disposable item, while the endoscope is sterilized between uses. Since the catheter is provided as a removable and disposable item, problems with steam sterilization are avoided which arise from the lack of steam penetration within the catheter

lumen. While steam sterilisation does not affect the endoscope as it is disposed with wider bore lumina, it would not be possible to sterilize the lumen of a catheter inserted into the endoscope channel owing to its narrow diameter. Thus the disposable pressure detection assembly of the invention overcomes this problem.

Advantageously, when the rinse inlet channel is used, fresh rinse medium continually washes over the pressure detecting body, removing or preventing blockages or contamination with particles. The assembly provides an economical solution to the problem, that can be deployed on existing endoscopes without significant adaptation.

[10] An example of a suitable catheter is the thin walled polyimide catheter (Microlumen®, Tampa, Florida) provided with or without a stainless steel braid . The body or outer wall of the proximal end or portion of the catheter is sealably connected to a coupling for the relevant endoscope rinse port which coupling is configured to fluidicly isolate the open proximal end of the catheter from the rinse port of the endoscope**.** The rinse port may be the rinse inlet port or the rinse outlet port**,** preferably the rinse inlet port**.**

3

VI3 Capillary Tube Assembly

United States Patent

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Date of filing: 26.07.2011
International publication number: WO 2012/013662

VI3.1 Field of the invention

The present invention relates to the field of invasive medical tubing, more specifically to catheters and lumbar puncture needles.

VI3.2 Background of the invention

VI3.2.1 Central venous catheters

During hospitalisation or a surgical procedure, there may be a need to swap a single lumen catheter to a multi-lumen or vice versa, for example, to provide an additional channel for pressure measurement or drug administration. Using present techniques, the existing catheter is typically removed over a guidewire, and the replacement catheter is fed over the same guidewire to the location of the previous catheter. Alternatively, a new puncture is performed to place a new catheter. Both procedures entails important risk. Notably, it is traumatic and can give rise to complications such as pneumothorax, hematothorax, nerve damage, accidental puncture of arteries, and stroke. Moreover, the handling of a second catheter leads to an increased risk of infection.

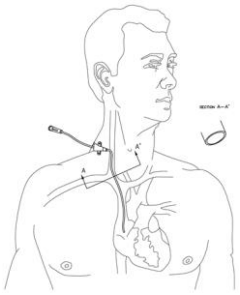

Figure 1: Central venous catheter placed in the jugular vein, with distal end in the right atrium.

VI3.2.2 Diagnostic procedure for hydrocephalus

Normal pressure hydrocephalus (NPH) is characterized by a triad of cognitive impairment, gait disturbance and nocturesis. The diagnosis is often difficult due to the symptoms being similar to other disorders such as dementia or Parkinson's disease. Many patients go completely unrecognized and are never treated. The condition is due to the fact the intracranial pressure (ICP) pressure is elevated. It has been confirmed that pressure is increased due to reduced absorption capacity. Therefore, a shunting device which drains the cerebro-spinal fluid (CSF) from the brain towards the abdomen or bloodstream is the principal therapy.

Several diagnostic procedures are currently used to make the diagnosis of NPH, which include magnetic resonance imaging (MRI), a lumbar puncture tap test (figure 4), or measurement of absorption capacity. For the latter, saline is infused into the CSF space while the pressure is measured. A steep rise in pressure indicates reduced absorption. Infusion is normally performed through a lumbar puncture needle while the pressure is monitored through a second lumbar puncture needle. Some neurosurgeons use one large diameter needle for both infusion and monitoring. Infusion and monitoring through one fine needle is impossible since the dynamic resistance causes a false increased pressure reading. The issue with multiple or large lumbar puncture needles is the discomfort for the patient and the higher risk of post puncture hypotension headache. In the case of a large diameter needle, the hole in the lumbar spinal dura caused by the puncture does not close spontaneously after measurement. In upright position the high hydrostatic pressure will cause an escape of CSF. The reduced pressure in the brain causes severe headaches.

There is thus a need for a device which can overcome the problems of the art.

VI3.3 Summary of some aspects of the invention

The invention relates to a detachable device for adding one or more channels to a bodily invasive tube, comprising a capillary tube assembly described herein. The invention relates to a capillary tube assembly having a proximal end and a distal end, comprising: a capillary tube shaft disposed with a capillary lumen extending from an open proximal end to an open distal end, and a fluidic adapter at the proximal end in fluid connection the capillary tube lumen, wherein the capillary tube shaft is adapted for dismountable insertion into a fluid-carrying lumen of a bodily invasive tube - such as a central venous catheter, a neuro-endoscope or a lumbar puncture needle -, and the adapter provides fluidic access to the capillary tube lumen that is fluidically isolated from access to the invasive tube lumen. The capillary tube shaft is preferably thin walled. The adapter may be configured for dismountable connection to a coupling on the invasive tube. The capillary tube shaft may be formed from polyimide. The device or capillary tube assembly may be packaged in an applicator comprising: a longitudinal protective cover having a proximal end and a distal end, an opening at the distal end, wherein the protective cover forms a void in which the capillary tube shaft and at least a distal part of the adapter are disposed, the cover is configured such that the capillary tube shaft is slidable relative to the opening at the distal end.

The protective cover may be comprised in a rigid, hollow protective tube having a breachable seal disposed along the longitudinal length of the wall of the tube, and the breachable seal may be configured to breach as the adapter is slidably advanced towards the intermediate coupling.

The capillary tube assembly may be employed as a hydrostatic pressure detector, for measuring the pressure at the distal tip of the invasive tube. The capillary tube lumen may be filled with a non-compressible fluid for example, a liquid such as aqueous saline solution. Hydrostatic pressure in the vicinity of the distal open end of the capillary tube is conducted along the lumen by the non-compressible fluid to the open proximal end of the capillary tube where a pressure gauge in dismountable fluidic connection with the lumen measures the pressure transmitted from the distal end of the capillary tube.

Advantageously, the capillary tube assembly provides a measurement of ambient pressure at the distal end of the invasive tube that accurately reflects the static pressure in the cavity (e.g. blood vessel, lumbar cavity, bladder etc.) into which the distal end of the invasive tube shaft is inserted.

VI3.3.1 Designated for lumbar infusion test

A clinician, wanting to diagnose normal pressure hydrocephalus using conventional techniques, will employ two lumbar puncture needles each inserted into the spinal lumbar cavity. One needle is used to inject a liquid medium (e.g. water) into the cavity while the second needle, attached to a pressure gauge, is employed to measure hydrostatic pressure in the cavity which corresponds to the intracranial pressure (ICP). Alternatively, measurement of

the ICP may be performed using a single large diameter needle for both infusion and measurement. The use of two needles or a larger needle leads to patient discomfort and an increased risk of side-effects. The use of a single fine needle and a gauge attached to a three way valve at the proximal end of the fine needle would severely overestimate the ICP. It is important that the ICP is measured reliably to allow the correct determination of the ICP as a function of the infusion rate, since this ratio has an important diagnostic value.

By employing the capillary tube assembly inserted into the needle used to inject liquid medium, a more accurate estimate of ICP is obtained, while the procedure requires the use only of a single lumbar puncture needle. The capillary tube assembly provides an economical solution to these problems, that can be deployed on existing invasive tube assemblies (e.g. multilumen catheter, lumbar puncture needle) without significant adaptation.

VI3.3.2 Designated for neuro-endoscopic procedures

The pressure measurement capability of the capillary tube assembly has application, for example, when the invasive tube is a multilumen catheter. In particular said catheter has a rinse inlet channel, for the introduction of rinse medium into the cavity and having a separate drainage outlet channel for the drainage of medium from the cavity. The catheter thus operates in a continuous flow irrigation mode.

VI3.3.3 Designated for central venous catheter system

Figure 3: Capillary tube assembly to reversibly upgrade a central venous catheter

The pressure measurement capability of the capillary tube assembly has application, for example, when the invasive tube is a central venous catheter (single channel or multi lumen). In many medical or surgical circumstances, close hemodynamic monitoring of the central venous pressure is essential. The central venous pressure (CVP) is the pressure of the blood in the caval veins, close to the heart. It is imperative to have a precise measurement of this pressure as it is essential for hemodynamic management of the most vulnerable patients. In clinical practice, the CVP is measured through a central venous catheter, where a channel is reserved only for measurement of this pressure. Sometimes, it is necessary to use this same channel for drug administration, however, this would inevitably cause an erroneous CVP-measurement because of the dynamical resistance (described by de Hagen-Poiseuille equation) of the lower part of the catheter system. The capillary tube assembly allows one channel of the catheter to have separate pressure measurement and drug delivery functions, without sacrificing accuracy of the CVP measurement.

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Curriculum Vitae

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° March 21, 1975 in Gent, Belgium

- Primary & high school: St.-Lievenscollege, Gent, 1986-1992.
- Medical degree : Ghent University, 1992-1999.
- Master of Medicine in Occupational Medicine, Ghent University, 2000 - 2002.
- Master of Science in Biomedical Engineering, Ghent University, 2000 - 2003.
- Master in Business Administration, Vlerick Business school, 2015
- PhD in Medical Sciences, Groningen, The Netherlands 2011
  Hemodynamic physiology during perioperative intracranial hypertension: Monitoring and therapeutic implications.
- Postgraduate course : Electrocardiography, Ghent University, 1997.
- Postgraduate course : Radiation protection & Radiation Physics, Ghent University, 1999.
- Postgraduate course : implementation of GCP directives for clinical drug research. Ghent University, 2004.
- Postgraduate course on Laboratory Animal Science – FELASA level C,
  UMC Groningen 2010
- Internship in Internal Medicine : Maria Middelares Hospital, Gent 1999-2000
- Resident in Anesthesiology and Resuscitation,
  Ghent University, 2002 - 2008.
- Fellowship in Cardiac Anesthesia OLV-Hospital, Aalst, Belgium 2008-2009
- Certificate level 1 experience in TEE : OLV-Hospital, Aalst 2009.
- Staff Anaesthetist University Medical Centre Groningen. 2009-2014
- Board member ESA Scientific Subcommittee : Equipment & Computers 2013-2015
- Clinical research director, Steerable Instruments 2010-present
- Principal investigator, University Medical Centre Groningen. 2013-present
- Staff Anaesthetist, Maria Middelares Hospital, Gent. 2014-present